07 CV 5915

JUDGE SCHEINDLIN

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICAL INDUSTRIES LTD. and TEVA PHARMACEUTICALS USA, INC.,	)	
Plaintiffs	)	Civil Action No.
v.	)	
MYLAN PHARMACEUTICALS, INC.,	)	
Defendant.	)	

JUN 21 2007

U.S.D.C. S.D. N.Y.
CASHIERS

COMPLAINT FOR DECLARATORY JUDGMENT

For their Complaint against Defendant Mylan Pharmaceuticals, Inc., ("Defendant"), Plaintiffs Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") and Teva Pharmaceuticals USA, Inc. ("Teva USA") allege as to their own acts, and on information and belief as to the acts of others, as follows:

THE PARTIES

1. Teva Ltd. is a corporation organized under the laws of Israel, and maintains its principal place of business at 5 Basel Street, Petah Tiqva 49131, Israel.

2. Teva USA is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva USA is a wholly-owned subsidiary of Teva Ltd.

3. On information and belief, Defendant is a West Virginia corporation with its principal place of business located at 781 Chestnut Ridge Road, Morgantown, West Virginia

26505. On Information and belief, Defendant is registered to do business in the State of New York and has registered agent "Corporation Service Company" located at 80 State Street, Albany, New York 12207

NATURE OF THE ACTION

4. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 1 et seq., and seeking injunctive relief under 35 U.S.C. §§ 281-283.

JURISDICTION AND VENUE

5. This Court has subject matter jurisdiction over this controversy under 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

6. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction.

7. This Court has personal jurisdiction over Defendant because Defendant is licensed to do business in the State of New York and continuously, systematically, and purposefully conducts business within this District, including but not limited to the business of developing, manufacturing, and selling various pharmaceutical products, many of which are marketed, distributed, and sold in New York.

8. Venue is proper in this judicial district based on 28 U.S.C. § 1400(b) and/or 28 U.S.C. § 1391(b), (c), and (d).

FACTUAL BACKGROUND

The Patents in Suit

9. Teva Ltd. is the owner of all right, title and interest in United States Patent Nos. 6,699,997 ("the '997 Patent"), 6,710,184 ("the '184 Patent"), 7,056,942 ("the '942 Patent"), and 7,126,008 ("the '008 Patent"; collectively, "the patents in suit") relating to, *inter alia*, various forms of a chemical compound known as carvedilol and processes for preparing various forms of carvedilol. One polymorphic form of carvedilol is known as "Form II."

10. The '997 Patent was duly and legally issued by the United States Patent and Trademark Office ("PTO") on March 2, 2004 for an invention entitled "Carvedilol." A copy of the '997 Patent is attached as Exhibit A.

11. The '008 Patent was duly and legally issued by the PTO on October 24, 2006 for an invention entitled "Carvedilol." A copy of the '008 Patent is attached as Exhibit B.

12. The '997 and '008 Patents claim processes for preparing carvedilol.

13. The '184 Patent was duly and legally issued by the PTO on March 23, 2004 for an invention entitled "Crystalline Solids of Carvedilol and Processes for Their Preparation." A copy of the '184 Patent is attached as Exhibit C.

14. The '184 Patent claims processes for preparing carvedilol Form II.

15. The '942 Patent was duly and legally issued by the PTO on June 6, 2006 for an invention entitled "Carvedilol." A copy of the '942 Patent is attached as Exhibit D.

16. The '942 Patent claims, *inter alia*, a hydrate form of carvedilol hydrochloride.

GlaxoSmithKline's Exclusivity

17. Carvedilol is a pharmaceutical compound used in the treatment of congestive heart failure. It is the active pharmaceutical ingredient ("API") in the product sold by GlaxoSmithKline ("GSK") under the trade name COREG®. COREG® is included in the United States Food and Drug Administration's ("FDA") list of "Approved Drug Products With Therapeutic Equivalence Evaluations," also known as the "Orange Book." Approved drugs listed in the Orange Book may be used as the basis of a later applicant's Abbreviated New Drug Application to obtain approval of the applicant's generic drug product under 21 U.S.C. § 355(j).

18. The carvedilol compound is disclosed and claimed in U.S. Patent No. 4,503,067 ("the '067 Patent"), which is owned by GSK. The '067 Patent is listed in the FDA's Orange Book in association with COREG®. The '067 Patent expired on March 5, 2007.

19. Pursuant to 21 U.S.C. § 355a, GlaxoSmithKline was awarded a six-month period of pediatric exclusivity following the expiration of the '067 Patent. GlaxoSmithKline's pediatric exclusivity period extends from March 5, 2007 to September 5, 2007. Pursuant to this exclusivity, the FDA cannot grant final approval to any Abbreviated New Drug Application ("ANDA") holders for carvedilol during that period. The FDA may grant final approval to ANDA holders beginning immediately upon expiration of GSK's pediatric exclusivity period.

Defendant's Imminent Infringement of the Patents in Suit

20. On information and belief, Defendant submitted ANDA No. 77-316 to the FDA, requesting approval to market a generic version of COREG® in 3.125, 6.25, 12.5 and 25 mg dosage strengths.

21. Defendant has received tentative approval of its ANDA from the FDA. On information and belief, final approval of Defendant's ANDA is expected to be granted shortly after the expiration of GSK's pediatric exclusivity period on September 5, 2007. Once Defendant receives final approval of its ANDA, it will be able to market generic carvedilol tablets in the United States.

22. Under the Hatch-Waxman Act, ANDA holders must provide detailed information to the FDA about how the API to be used in their proposed generic products will be made. ANDA holders may make the API themselves or, instead, may purchase the API from a supplier. When an ANDA holder intends to purchase API from a supplier to use in the proposed product, the ANDA holder may reference a Drug Master File submitted to the FDA by that supplier, instead of providing process information in the ANDA. Plaintiffs have been unable to obtain from a public source any information regarding whether Defendant will make or purchase the API to be used in its proposed products.

23. On information and belief, Defendant plans and intends to make carvedilol API or to purchase carvedilol API from a third party DMF holder, to use in the manufacture of its proposed generic carvedilol tablets ("Defendant's tablets").

24. On information and belief, Defendant plans and intends to engage in the commercial importation, manufacture, use, sale and/or offer for sale of generic carvedilol tablets in the United States.

25. On information and belief, Defendant plans and intends to engage in the activities described in paragraph 24 immediately upon receiving final approval of its ANDA from the FDA, and said approval will occur shortly after GSK's pediatric exclusivity period expires.

26. On information and belief, Defendant plans and intends to engage in the activities described in paragraph 24 prior to the expiration of the patents in suit.

27. On information and belief, Defendant's tablets will include carvedilol API that infringes or will infringe one or more claims of the patents in suit, and/or that is or will be made by a process that infringes one or more claims of the patents in suit. Accordingly, Defendant's plans and intentions to make and sell carvedilol tablets in the United States constitute imminent, threatened acts of infringement under 35 U.S.C. § 271, which give rise to an actual controversy over which the Court may exercise jurisdiction.

28. Plaintiffs have made a reasonable effort to determine the chemical composition of the carvedilol API to be used in Defendant's tablets, as well as the process by which the carvedilol API to be used in Defendant's tablets is or will be made. On May 8, 2007, Teva USA notified Defendant of the existence of the patents in suit and sought information allowing Plaintiffs to ascertain whether Defendant's tablets and/or the API to be used in Defendant's tablets fall within the scope of one or more of the patents in suit, and/or whether the API to be used in Defendant's tablets is made pursuant to a process that falls within the scope of one or more of the patents in suit. In particular, Teva USA requested a detailed description of all processes that will be used to manufacture Defendant's tablets, all processes that will be used to make the API to be used in Defendant's tablets, samples of Defendant's tablets, and samples of the API to be used in Defendant's tablets. Teva USA offered to enter into a confidentiality agreement to protect the confidentiality of any information disclosed by Defendant. Pursuant to this offer, Teva USA supplied a proposed confidentiality agreement to Defendant.

29. Defendant has not provided to Teva USA samples of Defendant's tablets or of the API to be used in Defendant's tablets, or the detailed information requested regarding the processes by which Defendant's tablets are manufactured or the API to be used in the tablets is made, despite Teva USA's offer of confidentiality. Further, Plaintiffs have been unable to obtain from a public source samples of Defendant's tablets or the API to be used in their manufacture.

30. Without the requested information, Plaintiffs are unable to determine whether Defendant's tablets, or the API to be used in Defendant's tablets, infringes one or more compounds claimed in the patents in suit, or whether the processes by which the API is made infringe one or more methods claimed in the patents in suit. For this reason, Plaintiffs cannot conclusively determine whether Defendant infringes each of the patents in suit unless and until Defendant provides samples of its tablets and samples of the API to be used in their manufacture and discloses to Plaintiffs the processes by which the tablets and API are made.

31. In the absence of a sufficient response from Defendant, Plaintiffs have no choice but to resort to the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, the information required to confirm their beliefs as to infringement and to present the Court evidence that Defendant will infringe the patents in suit.

32. As a direct and proximate consequence of the planned and intended infringement by Defendant, Plaintiffs will be injured in their business and property rights unless the infringement is enjoined by the Court, and will suffer injury for which they are entitled to relief.

COUNT I

Declaratory Judgment of Patent Infringement

33. Plaintiffs repeat and reallege Paragraphs 1 through 32 of the Complaint as if fully set forth herein.

34. On information and belief, the importation, manufacture, use, sale and/or offer for sale by Defendant of its carvedilol tablets pursuant to ANDA No. 77-316 will infringe, either literally or under the doctrine of equivalents, one or more claims of the '997, '184, '942, and/or '008 Patents, or will contribute to or induce such infringement, under 35 U.S.C. § 271.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs Teva Ltd. and Teva USA respectfully request a judgment from the Court:

1. Declaring that the '997, '184, '942, and '008 Patents are valid and enforceable;

2. Declaring that Defendant will infringe, either literally or under the doctrine of equivalents, one or more claims of the '997, '184, '942, and/or '008 Patents, or will contribute to or induce such infringement, under 35 U.S.C. § 271;

3. Declaring that Defendant's infringement will be willful and that this is an exceptional case under 35 U.S.C. § 285;

4. Permanently enjoining Defendant, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringing the '997, '184, '942, and '008 Patents;

5. Awarding Plaintiffs their attorneys' fees, costs, and expenses; and

6. Awarding Plaintiffs such other relief that the Court deems proper, just and equitable.

Respectfully submitted this 21st day of June, 2007.

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Exhibit A

US006699997B2

(12) **United States Patent**
Hildesheim et al.

(10) **Patent No.: US 6,699,997 B2**
(45) **Date of Patent: Mar. 2, 2004**

(54) **CARVEDILOL**

(75) Inventors: **Jean Hildesheim**, Mazkeret Batya (IL); **Sergey Finogueev**, Quiriat Arbaa (IL); **Ben-Zion Dolitzky**, Petach Tikva (IL); **Shoshana Ben-Valid**, Sderot (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/894,798**

(22) Filed: **Jun. 28, 2001**

(65) **Prior Publication Data**

US 2002/0143045 A1 Oct. 3, 2002

Related U.S. Application Data

(60) Provisional application No. 60/214,356, filed on Jun. 28, 2000, and provisional application No. 60/246,358, filed on Nov. 7, 2000.

(51) **Int. Cl.**[7] **C07D 209/82**
(52) **U.S. Cl.** **548/444**
(58) **Field of Search** 548/444; 514/411

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,503,067 A 3/1985 Wiedemann et al.
5,071,868 A * 12/1991 Leinert et al.

FOREIGN PATENT DOCUMENTS

EP 0 127 099 B1 5/1987
EP 0 918 055 5/1999
WO W099/05105 2/1999

OTHER PUBLICATIONS

G.M. Wall, "Pharmaceutical Applications of Drug Crystal Studies", Pharmaceutical Manufacturing, vol. 3, No. 2, pp. 33–42, Feb. 1986.

J.K. Haleblian and W. McCrone , "Pharmaceutical Applications of Polymorphism", Journal of Pharmaceutical Sciences, vol. 58, No. 8, pp. 911–929, Jul. 1969.

J.K. Haleblian, "Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications", Journal of Pharmaceutical Sciences, vol. 64, No. 8, pp. 1269–1288, Jul. 1975.

Pharmacopeial Forum, vol. 24, No. 1, pp. 5438–5441, Jan. –Feb. 1998.

Senderoff et al., "Synthesis of the Enantiomers and Three Racemic Metabolites of Carvedilol Labeled to High Specific Activity With Tritium", Jouranl of Labeled Compounds and Radiopharmaceuticals, Dec. 1993, vol. 33, No. 12, pp. 1091–1105.

* cited by examiner

Primary Examiner—Joseph K. McKane
Assistant Examiner—Kamal Saeed
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof.

19 Claims, 7 Drawing Sheets

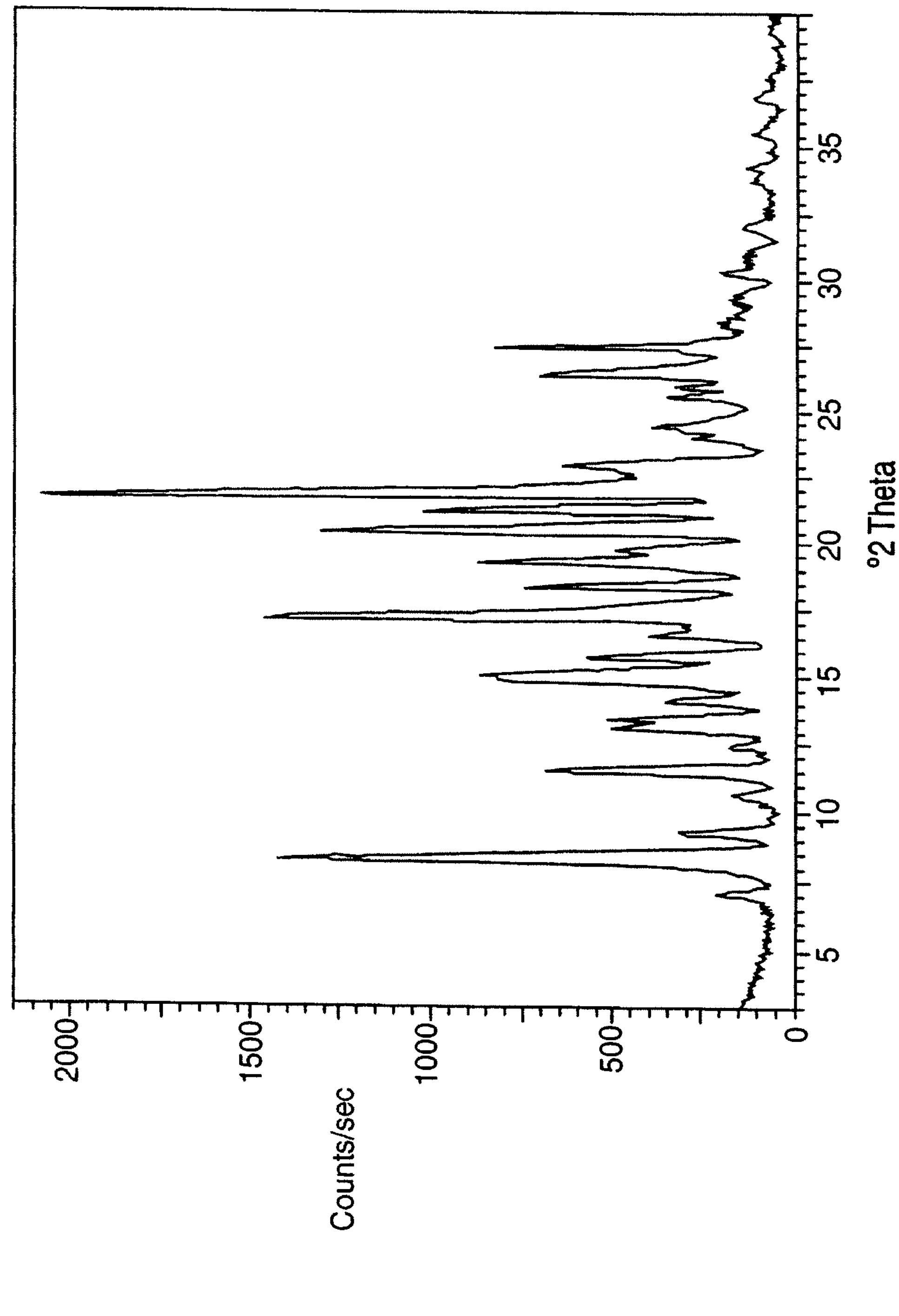

FIG. 1

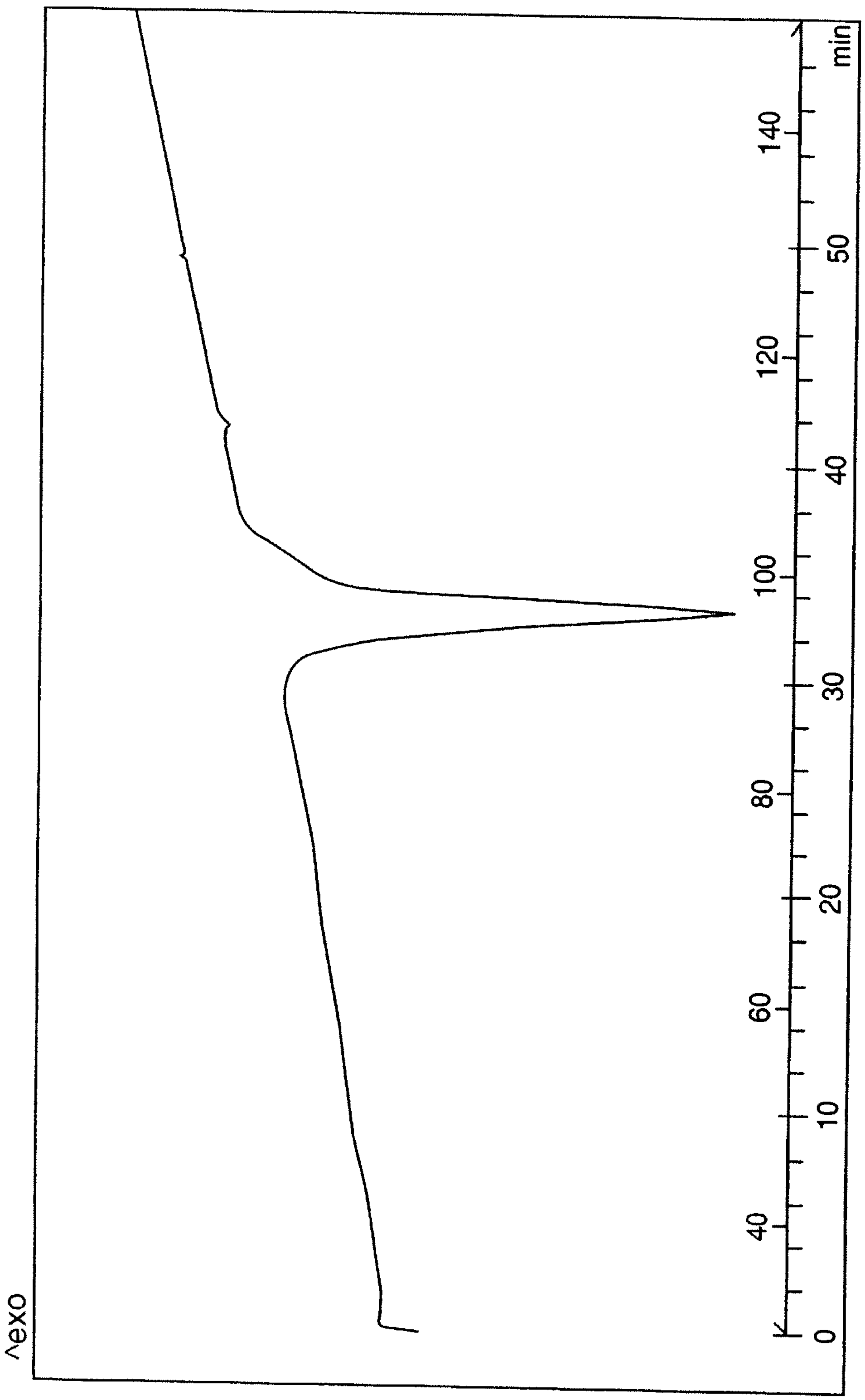

FIG. 2

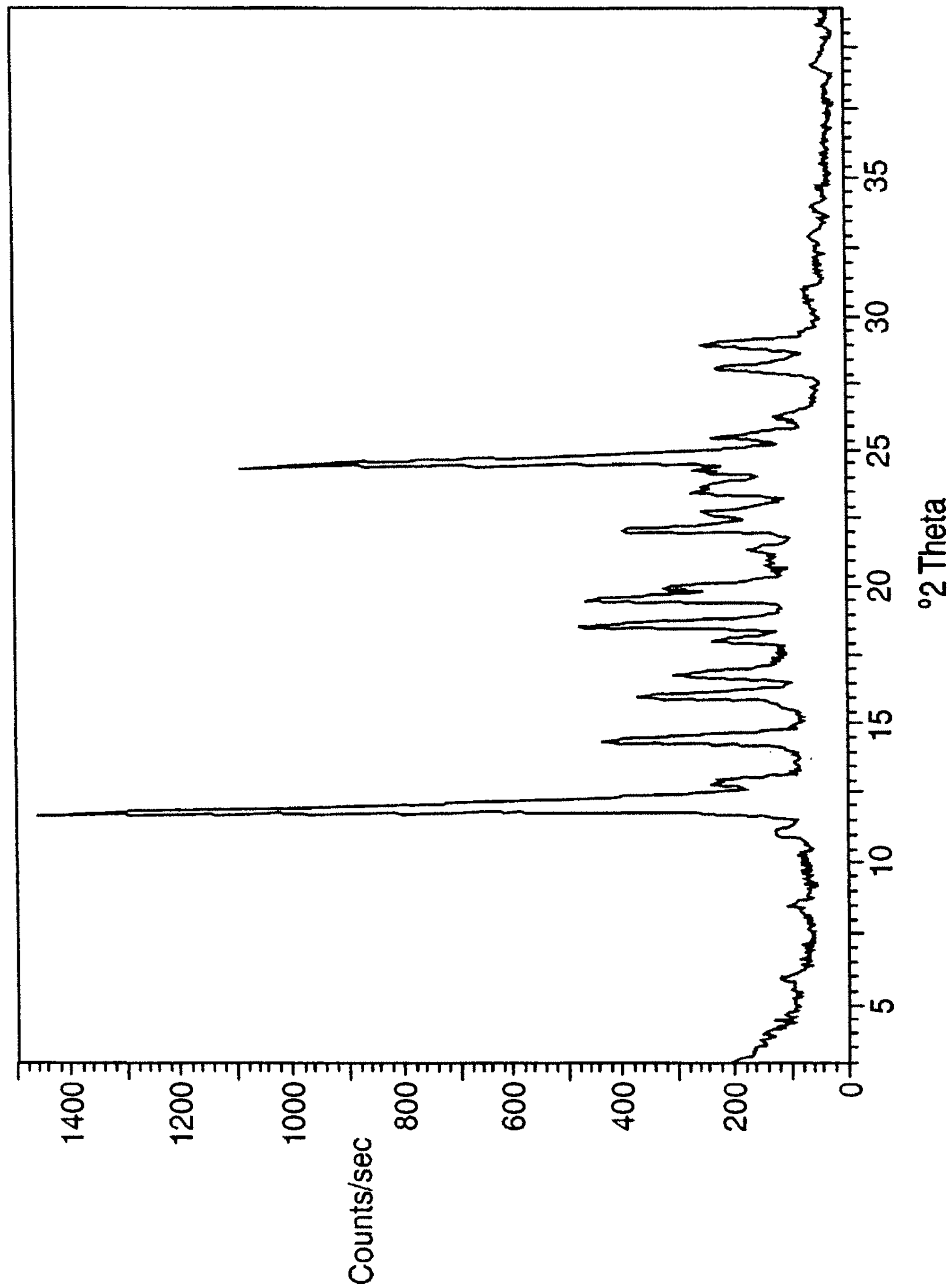
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FIG. 3

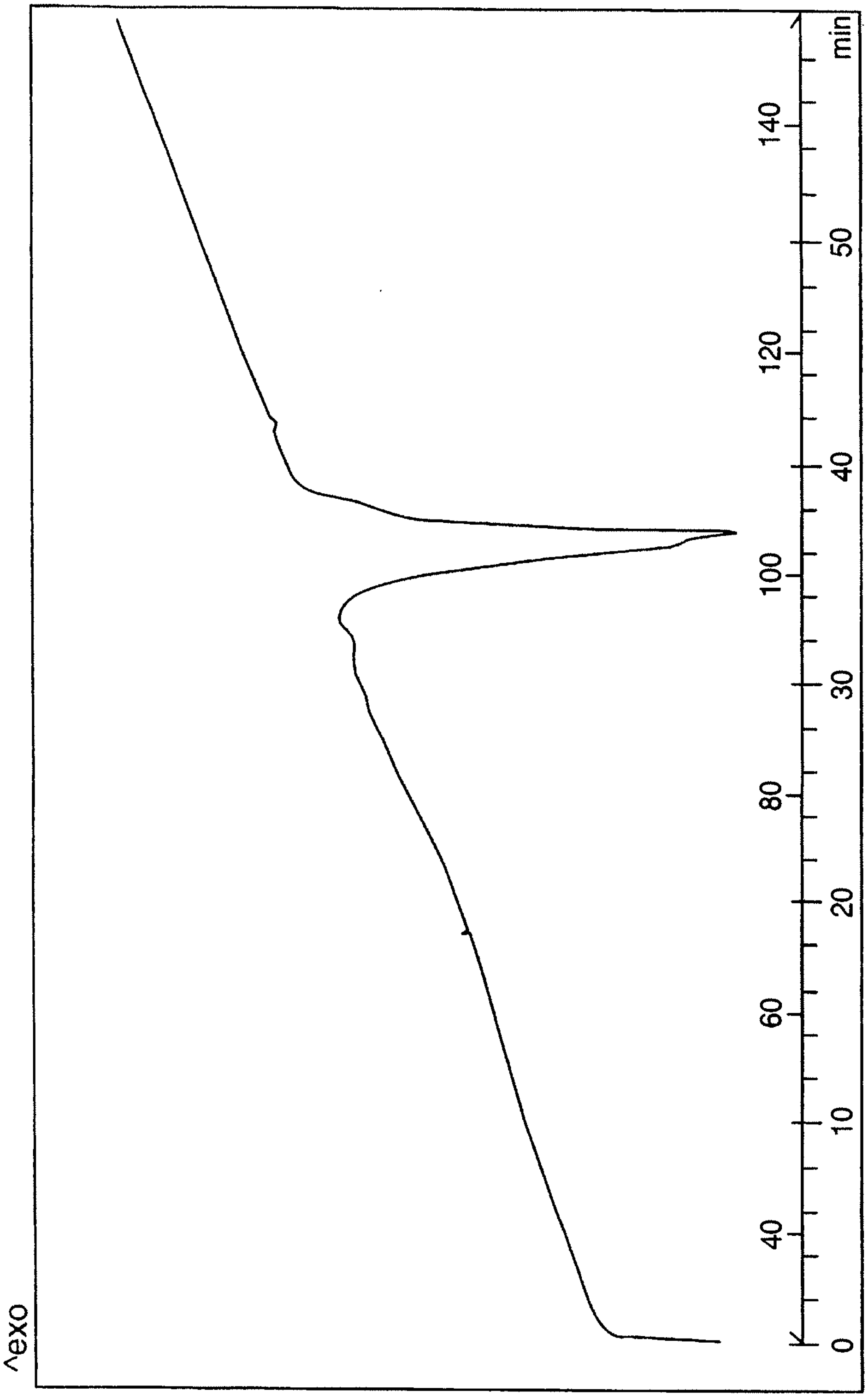

FIG. 4

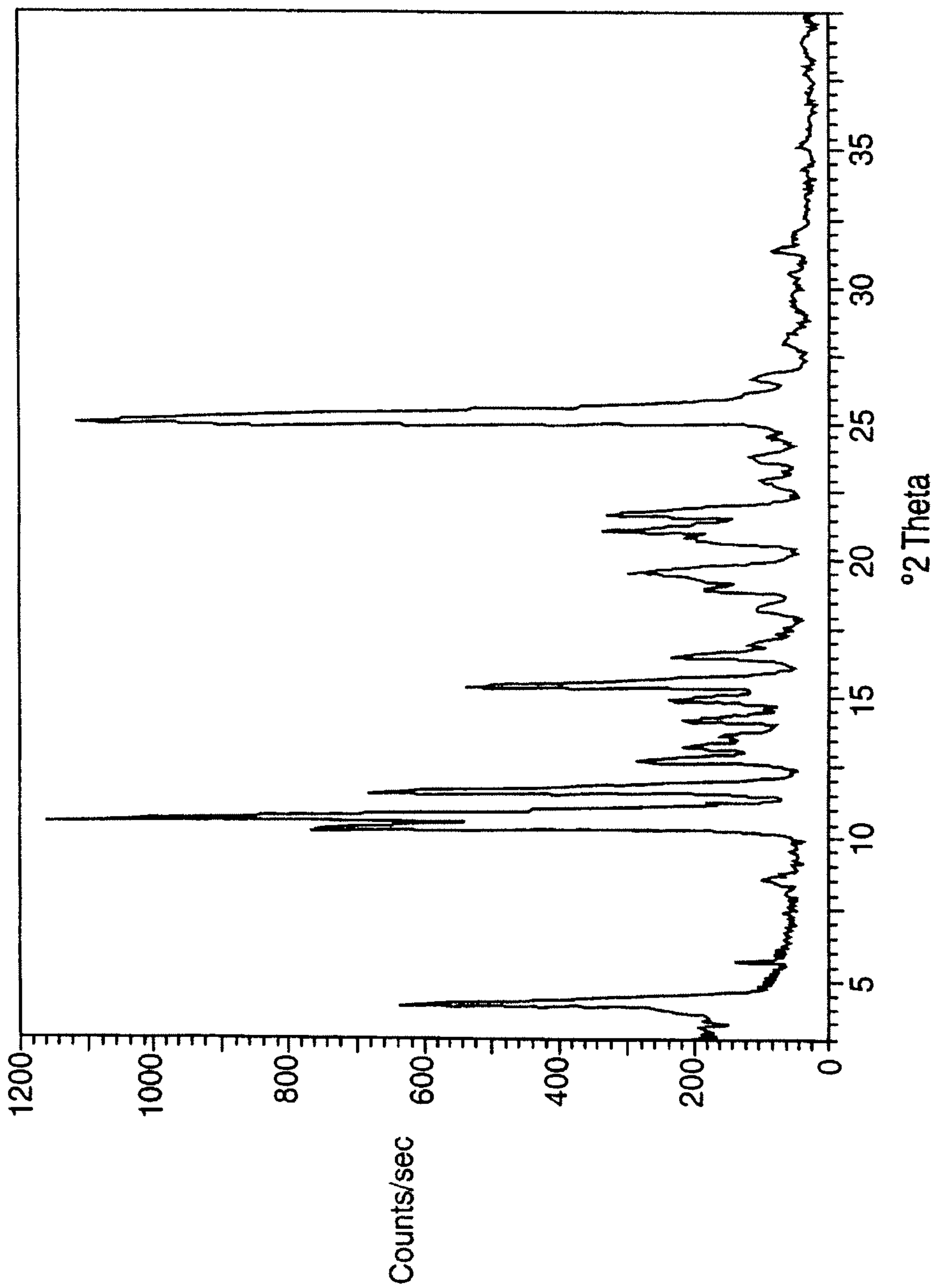

FIG. 5

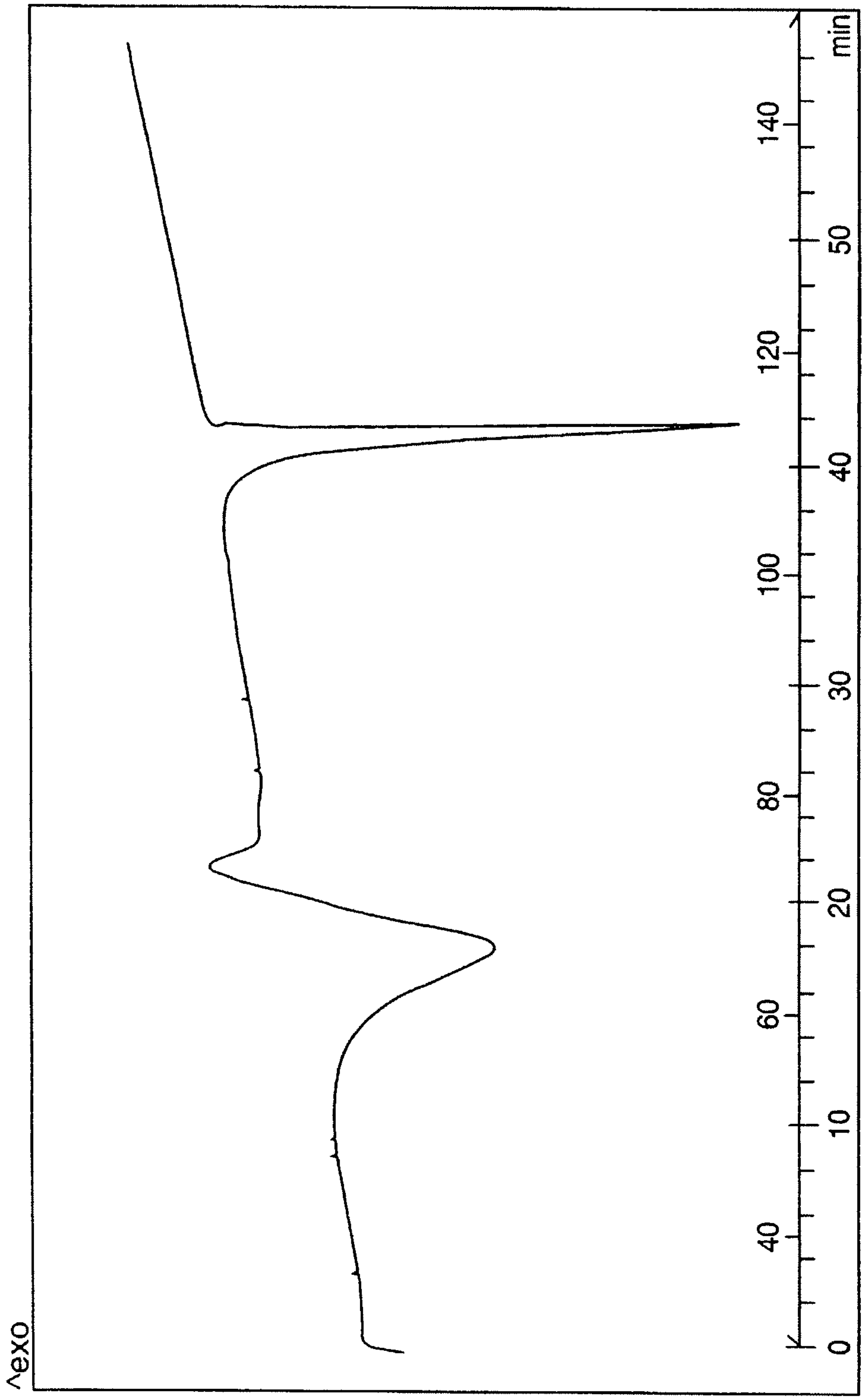

FIG. 6

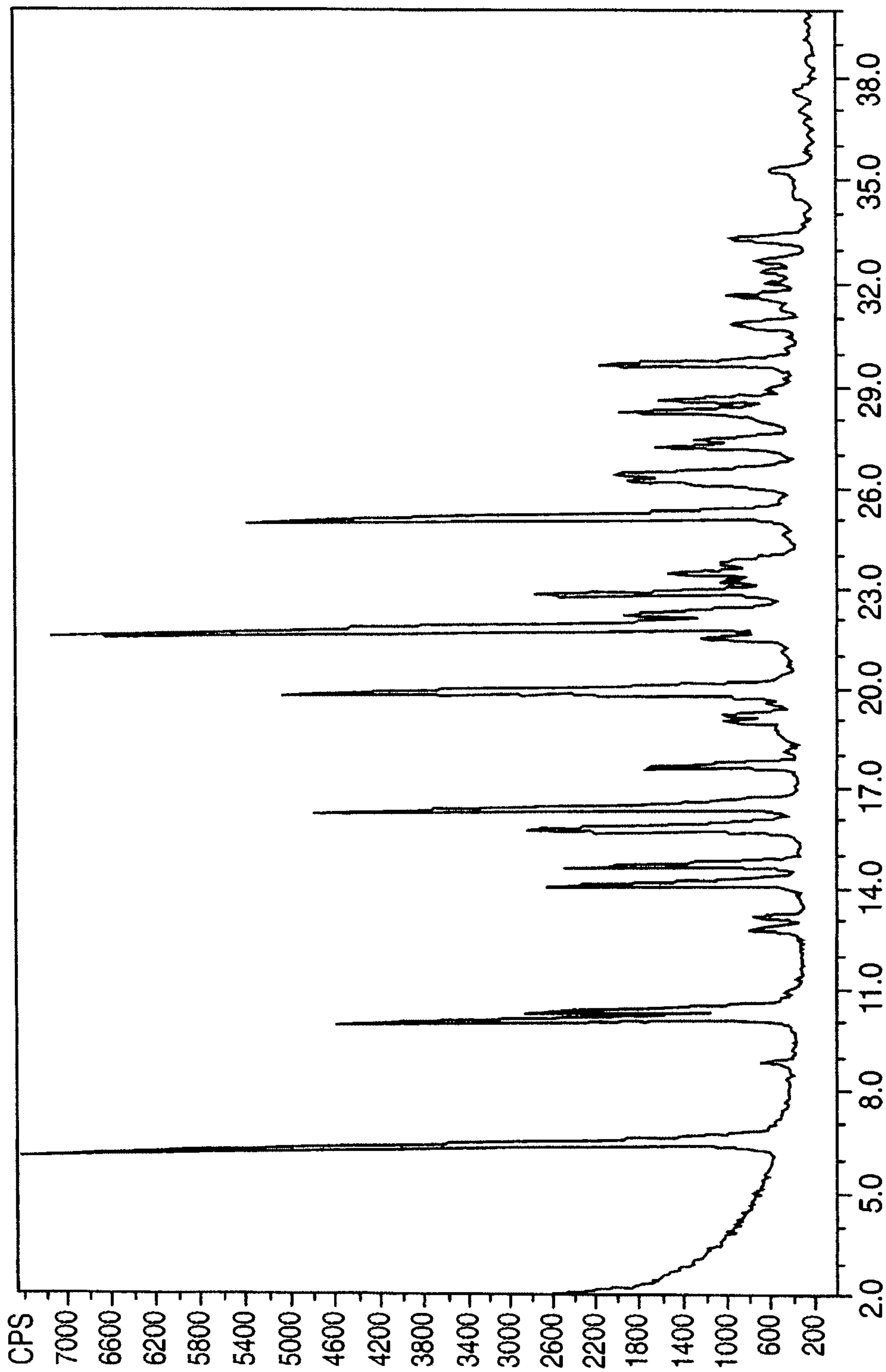
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FIG. 7

CARVEDILOL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional applications Nos. 60/214,356, filed Jun. 28, 2000 and 60/246,358, filed Nov. 7, 2000, incorporated herein by reference.

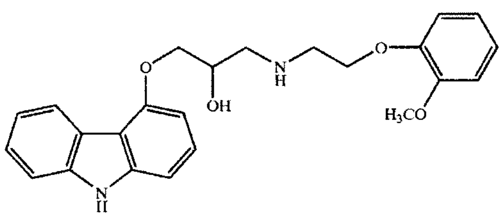
FIELD OF THE INVENTION

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1 blocking activity. Carvedilol, also known as (±)1-(9H-carbazol-4-yloxy)-3-[[2(2-methoxyphenoxy)ethyl]amino]-2-propanol, (CAS Registry No. 72956-09-3) has the structure of formula I.

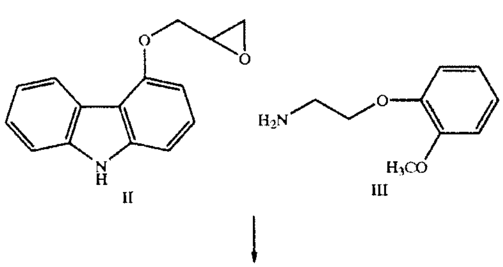
I



Carvedilol has a chiral center and can exist either as individual stereoisomers or in racemic form. Racemic carvedilol is the active ingredient of COREG®, which is indicated for the treatment of congestive heart failure and hypertension. The nonselective β-adrenergic activity of carvedilol is present in the S(−) enantiomer and the α_1 blocking activity is present in both the R(+) and S(−) enantiomers at equal potency. Both the racemate and stereoisomers may be obtained according to procedures well known in the art (EP B 0127 099).

Synthesis of Carvedilol

U.S. Pat. No. 4,503,067, which is incorporated herein by reference, discloses a process of preparing carvedilol by the following reaction:



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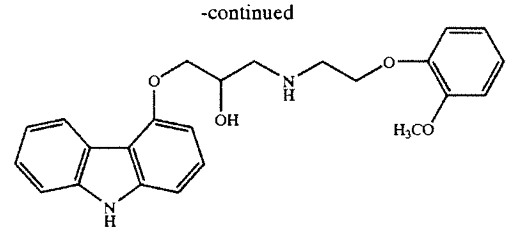
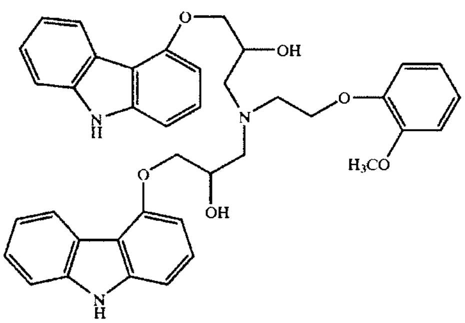


I

in which 4-(oxiran-2-ylmethoxy)-9H-carbazole (formula II) is reacted with (2-(2-methoxyphenoxy)ethylamine (formula III) to form carvedilol (I). The above process produces a low yield of carvedilol at least in part because in addition to carvedilol, the process leads to the production of a bis impurity of the following structure (formula IV):

IV



(See EP 918055.)

In order to reduce the formation of the formula IV and to increase the yield of carvedilol, EP 918055 discloses using a benzyl protected form of the 2-(2-methoxyphenoxy) ethylamine (III).

Carvedilol Polymorphs

International application No. WO 99/05105, incorporated herein by reference, discloses that carvedilol can be isolated as two polymorphic forms, depending on the method of preparation. The two polymorphic forms, designated Form I and Form II, are reported to be monotropic and are distinguishable by their infrared, Raman and X-ray powder diffraction spectra. No evidence is found in the literature about the existence of hydrated solvate states of carvedilol.

Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline form in the solid state. A single molecule may give rise to a variety of crystal forms (also called "polymorphs", "hydrates" or "solvates") having distinct physical properties. For a general review of polymorphs and the pharmaceutical applications of polymorphs see G. M. Wall, *Pharm Manuf.* 3, 33 (1986); J. K. Haleblian and W. McCrone, *J. Pharm. Sci.*, 58, 911 (1969); and J. K. Haleblian, *J. Pharm. Sci.*, 64, 1269 (1975), all of which are incorporated herein by reference.

The existence and physical properties of different crystal forms can be determined by a variety of techniques such as X-ray diffraction spectroscopy, differential scanning calorimetry and infrared spectroscopy. Differences in the physical properties of different crystal forms result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly,

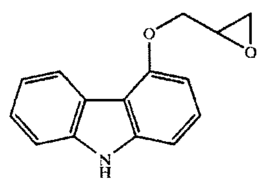
polymorphs, hydrates and solvates are distinct solids sharing the same molecular formula yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family. The existence and physical properties of polymorphs, hydrates and solvates is unpredictable.

One of the most important physical properties of a pharmaceutical compound which can form polymorphs, hydrates or solvates, is its solubility in aqueous solution, particularly the solubility in gastric juices of a patient. Other important properties relate to the ease of processing the form into pharmaceutical dosages, such as the tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet.

SUMMARY OF THE INVENTION

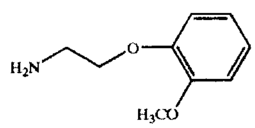
The present invention provides a process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,

II



with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine

III



wherein the compound of formula III is at a molar excess over the compound of formula II.

The present invention further provides crystalline carvedilol hydrate.

The present invention further provides crystalline carvedilol.

The present invention further provides crystalline carvedilol (methyl-ethyl-ketone) solvate.

The present invention further provides crystalline carvedilol Form III characterized by an X-ray powder diffraction pattern having peaks at about 8.4±0.2, 17.4±0.2, and 22.0±0.2 degrees two-theta.

The present invention further provides crystalline carvedilol Form IV characterized by an X-ray powder diffraction pattern having peaks at about 11.9±0.2, 14.2±0.2, 18.3±0.2, 19.2±0.2, 21.7±0.2, and 24.2±0.2 degrees two-theta.

The present invention further provides crystalline carvedilol (methyl-ethyl-ketone) solvate Form V characterized by an X-ray powder diffraction pattern having peaks at about 4.1±0.2, 10.3±0.2, and 10.7±0.2 degrees two-theta.

The present invention further provides carvedilol HCl Hydrate characterized by an X-ray powder diffraction pattern having peaks at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2, 16.4±0.2 and 22.2±0.2 degrees two-theta.

The present invention further provides a method for preparing crystalline carvedilol Form I, comprising the steps of dissolving carvedilol in a solution by heating; heating the solution until the crystalline carvedilol is completely dissolved; reducing the temperature of the solution; agitating the solution for a period of time; further reducing the temperature of the solution; further agitating the solution for a period of time; and collecting crystalline carvedilol Form I.

The present invention further provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent; precipitating carvedilol Form II by cooling the solution; and, isolating crystalline carvedilol Form II.

The present invention further provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent mixture; precipitating carvedilol Form II by cooling the solution to about −20° C.; and, isolating crystalline carvedilol Form II.

The present invention further provides a method for preparing crystalline carvedilol Form III, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating crystalline carvedilol Form III from the solvent solution using water as an anti-solvent.

The present invention further provides a method for preparing crystalline carvedilol Form III, comprising the steps of dissolving carvedilol in a solution by heating; cooling the solution mixture; and, collecting crystalline carvedilol Form III.

The present invention further provides a method for preparing crystalline carvedilol Form IV, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; adding an anti-solvent to the solvent solution; and, precipitating crystalline carvedilol Form IV from the solvent solution.

The present invention further provides a method for preparing crystalline carvedilol Form V, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating and isolating crystalline carvedilol Form V from the solvent solution.

The present invention further provides a method for preparing crystalline carvedilol Form V, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating and isolating crystalline carvedilol Form V from the solvent solution wherein the precipitation step is performed by adding an anti-solvent.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. shows the X-ray diffraction pattern of carvedilol Form III.

FIG. 2. shows the DTG thermal profile of carvedilol Form III.

FIG. 3. shows the X-ray diffraction pattern of carvedilol Form IV.

FIG. 4. shows the DTG thermal profile of carvedilol Form IV.

FIG. 5. shows the X-ray diffraction pattern of carvedilol Form V.

FIG. 6. shows the DTG thermal profile of carvedilol Form V.

FIG. 7. shows the X-ray diffraction pattern of carvedilol HCl.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "carvedilol" includes hydrates and solvates of carvedilol. The term "water content" refers

to the content of water, based upon the Loss on Drying method (the "LOD" method) as described in Pharmacopeia Forum, Vol. 24, No. 1, p. 5438 (Janurary–February 1998), the Karl Fisher assay for determining water content or thermogravimetric analysis (TGA). The term "equivalents of water" means molar equivalents of water. All percentages herein are by weight unless otherwise indicated. Those skilled in the art will also understand that the term "anhydrous", when used in reference to carvedilol, describes carvedilol which is substantially free of water. One skilled in the art will appreciate that the term "hemihydrate", when used in reference to carvedilol, describes a crystalline material having a water content of about 2.2% w/w. One skilled in the art will appreciate that the term "hydrate", in reference to carvedilol hydrochloride a crystalline material having a water content of about or above 2% w/w. One skilled in the art will also appreciate that the term "solvate of methyl-ethyl-ketone" refers to carvedilol in which solvent is contained within the crystal lattice in quantities above 1%. One skilled in the art will also appreciate that the term "solvate of methyl-ethyl-ketone" which contains one mole of is characterized by a methyl-ethyl-ketone content of about 14% by weight.

Hydrate and solvate forms of carvedilol are novel and distinct from each other in terms of their characteristic powder X-ray diffraction patterns and their thermal profiles.

For the purposes of this specification, ambient temperature is from about 20° C. to about 25° C.

All powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer. Copper radiation of λ=1.5418 Å was used.

Measurement of thermal analysis are conducted for the purpose of evaluating the physical and chemical changes that may take place in a heated sample. Thermal reactions can be endothermic (e.g., melting, boiling, sublimation, vaporization, desolvation, solid-solid phase transitions, chemical degradation, etc.) or exothermic (e.g., crystallization, oxidative decomposition, etc.) in nature. Such methodology has gained widespread use in the pharmaceutical industry in characterization of polymorphism. Thermal measurements have proven to be useful in the characterization of polymorphic systems. The most commonly applied techniques are thermogravimetry (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC).

The DTA and TGA curves presented herein were obtained by methods known in the art using a DTG Shimadzu model DTG-50 (combined TGA and DTA). The weight of the samples was about 9 to about 13 mg. The samples were scanned up to about 300° C. or above at a rate of 10° C./min. Samples were purged with nitrogen gas at a flow rate of 20 ml/min. Standard alumina crucibles covered lids with one hole.

Thermogravimetry analysis (TGA) is a measure of the thermally induced weight loss of a material as a function of the applied temperature. TGA is restricted to transitions that involve either a gain or a loss of mass, and it is most commonly used to study desolvation processes and compound decomposition.

Karl Fisher analysis, which is well known in the art, is also used to determine the quantity of water in a sample.

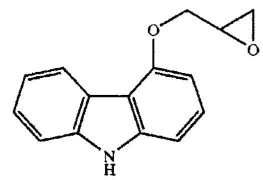
As used herein, a solvent is any liquid substance capable of dissolving carvedilol. As used herein, the term "anti-solvent" means a liquid in which a compound is poorly soluble. The addition of an anti-solvent to a solvent reduces the solubility of a compound. As used herein a mixture of solvents refers to a composition comprising more than one solvent.

As used herein, the term "neat" conditions refers to conditions of a reaction wherein the solvent of the reaction is one of the reactants.

Synthesis of Carvedilol

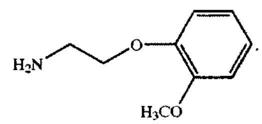
According to one embodiment, the present invention is a process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,

II



with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine

III



The new procedure results in a higher yield of carvedilol than has been reported in the prior art. In addition, the product of the new procedure is nearly free of bis impurities and the reaction is more rapid.

Preferably, the compound of formula III is at a molar excess over the compound of formula II. The compound of formula III and the compound of formula II are preferably at a molar ratio from about 1.5:1 to about 100:1. More preferably, the compound of formula III and the compound of formula II are at a molar ration from about 2.8:1 to about 10:1. Most preferably, the compound of formula III and the compound of formula II are at a molar ratio from about 2.8:1 to about 6:1.

In one embodiment of the present invention, the reacting step is performed in a solvent. The solvent is preferably selected from the group consisting of toluene, xylene and heptane. In an alternative embodiment, the reacting step is performed in a solvent mixture wherein the solvent mixture comprises multiple solvents. Preferably, a solvent of the solvent mixture is selected from the group consisting of toluene, xylene and heptane.

The reacting step is preferably performed at a temperature from about 25° C. and about 150° C. Most preferably, the reacting step is performed at a temperature from about 60° C. and about 120° C.

In an alternative embodiment, the reacting step is performed under neat conditions. The neat conditions may obtained by melting a solid form of the compound of formula III to form a liquid and, dissolving the compound of formula II in the liquid to form a reaction mixture.

The reaction performed under neat conditions may further comprise a step of reducing the temperature of the reaction mixture after dissolving the compound of formula II. The temperature is preferably reduced to about 70° C.

The reaction performed under neat conditions may further comprise a step of adding an organic solvent: water mixture to the reaction mixture. The organic solvent is preferably selected from the group consisting of ethyl acetate, methyl isobutyl ketone, methyl ethyl ketone and butyl acetate.

The reaction performed under neat conditions may further comprise a step of adjusting the pH of the organic solvent-:water mixture after it is added to the reaction mixture. The pH is preferably adjusted to less than about pH 5. More preferably, the pH is adjusted from about pH 3 to about pH 5.

Optionally, the process further comprises the steps of isolating carvedilol hydrochloride after adjusting the pH, and purifying carvedilol.

Carvedilol hydrochloride is optionally isolated as a hydrate. Carvedilol HCl isolated as a hydrate typically has an XRD peaks are found at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 14.2±0.2, 14.7±0.2, 16.4±0.2, 17.7±0.2, 20.0±0.2, 21.9±0.2, 25.2±0.2 degrees to 2-theta.

The reaction preformed under neat conditions may further comprise steps of, isolating carvedilol from the reaction mixture after adjusting the pH, and purifying carvedilol. Optionally, carvedilol may be purified by methods well known in the art. (See EP B 0127 099.)

Novel Methods for Preparing Crystalline Carvedilol Form I and Form II

One aspect of the present invention provides a method for preparing crystalline carvedilol Form I, by dissolving carvedilol in a solvent until the crystalline carvedilol is completely dissolved, reducing the temperature of the solution and agitating the solution for a period of time, further reducing the temperature of the solution and agitating the solution for a period of time and, collecting crystalline carvedilol Form I.

The dissolving step is optionally performed by heating the solvent.

The dissolving step is optionally performed by heating crystalline carvedilol at a temperature from about 50° C. 0 to about 60° C. for about 6 hours.

The dissolving step is optionally performed by suspending the crystalline carvedilol in ethyl acetate.

The dissolving step is optionally performed by heating the solution to about 77° C.

The step of reducing the temperature of the solution is optionally performed by cooling the solution to about 50° C. in a time period of 15 min.

The step of agitating solution is optionally performed at about 50° C. for about 48 hours.

The step of further reducing the temperature of the solution is optionally performed by cooling the solution to about 10° C. in about 0.75 hours with agitation.

The step of further agitating the solution is optionally performed by stirring the suspension for more than 5 hours. The step of further agitation may optionally be performed by stirring the suspension for about 24 hours.

The drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C. 0 to about 60° C. for about 6 hours.

The suspending step may be performed by suspending the crystalline carvedilol in ethyl acetate.

The heating step may be performed by heating the solution to about 77° C.

Another aspect of the present invention provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent, precipitating carvedilol Form II by cooling the solution, and isolating crystalline carvedilol Form II.

Optionally, the step of dissolving carvedilol is performed at a temperature from about 40° C. to about the boiling temp of the solvent.

Optionally, the step of cooling the solution is performed by reducing the temperature from about −20° C. to about ambient temperature.

Optionally, the solvent is selected from the group consisting of methanol, absolute ethanol, 1-propanol, isopropanol, n-butanol, ethylene glycol, butyl acetate, isobutyl methyl ketone, dichloromethane, dichloroethane, acetonitrile, acetone, isoamylalcohol, xylene and toluene.

Optionally, the precipitated carvedilol Form II is isolated by filtration.

Another aspect of the present invention provides a method for preparing crystalline carvedilol Form II, comprising the steps of: forming a solution of carvedilol by dissolving carvedilol in a solvent mixture, precipitating carvedilol Form II by cooling the solution to about −20° C., and isolating crystalline carvedilol Form II.

Optionally, the carvedilol is dissolved in a solution at a temperature from about 40° C. to about the boiling temperature of the solvent.

Optionally, the carvedilol Form II is isolated by filtration.

Optionally, the step of cooling the reaction is performed by cooling the solution to a temperature from about −20° C. to ambient temperature.

Optionally, the solvent mixture is selected from the group consisting of acetone:cyclohexane, chloroform:cyclohexane, dichloroethane:cyclohexane, dichloromethane:cyclohexane, pyridine:cyclohexane, tetrahydrofurane:cyclohexane, dioxane:cyclohexane, acetone:hexane, chloroform:hexane, dichloroethane:hexane, dichloromethane:hexane, tetrahydrofuran:hexane and ethanol:hexane.

Novel Carvedilol Polymorphs

In another aspect the present invention provides new crystalline forms of carvedilol, designated Forms III, IV, V and processes for the manufacture thereof. Moreover, the present invention provides a new hydrate form of carvedilol, having water content of about 2% by weight and processes for their manufacture. In another embodiment, the present invention provides new solvate forms of carvedilol, having solvent content up to about 14% by weight, wherein the solvent is methyl ethyl ketone, and processes for their manufacture. These hydrate/solvate forms of carvedilol are useful as intermediates for the synthesis of carvedilol drug substances.

Procedures for Crystallizing Novel Forms of Carvedilol

The novel hydrates/solvates forms provided herein are optionally formed by precipitating carvedilol as a crystalline solid from a solvent or a solvent mixture. It will be understood by those of skill in the art, that other methods may also be used to form the hydrate/solvates form disclosed herein. Alternatively the polymorphs may be formed by routine modification of the procedures disclosed herein.

Formation of Crystalline Carvedilol Form III

One embodiment of the present invention provides a method for preparing crystalline carvedilol Form III, which comprises the steps of forming a solvent solution containing carvedilol; and, precipitating crystalline carvedilol Form III from the solvent solution using water as an anti-solvent. The invention provides for a dissolving step wherein water is present in the solvent solution during the dissolving step. The invention also provides for a precipitation step wherein water is added to the solution after carvedilol is fully dissolved in a solvent.

Optionally, to form the solvent solution containing carvedilol, carvedilol may be dissolved in a solvent at elevated temperature. The preferred elevated temperature is from about 40 to about 90° C. Most preferably the elevated temperature is about 55° C. Alternatively, carvedilol may be dissolved in a solvent at ambient temperature.

Another embodiment of the present invention provides, forming the solvent solution containing carvedilol, by dis-

solving carvedilol in a solvent and inducing precipitation of crystalline carvedilol Form III by the addition of an anti-solvent. Solvents are optionally selected from the group which includes pyridine, dioxane, isopropanol and chloroform. Anti-solvents are optionally selected from the group which includes water and hexane.

An alternative embodiment of the present invention provides, forming the solvent solution containing carvedilol by dissolving carvedilol in an organic solvent and water and precipitating crystalline carvedilol Form III. In this embodiment the organic solvent is optionally an alcohol. The alcohol is preferably selected from the group consisting of methanol and ethanol. Alternatively, the organic solvent may be selected from the group of solvents consisting of pyridine, dioxane, and ethyl acetate and tetrahydrofurane.

An alternative embodiment of the present invention provides, a method for preparing crystalline carvedilol Form III, comprising the steps of: drying crystalline carvedilol at elevated temperature, suspending crystalline carvedilol in a solution mixture, heating the solution mixture until the crystalline carvedilol is completely dissolved, cooling the solution mixture, and collecting crystalline carvedilol Form III.

Optionally, the drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

Optionally, the suspending step may be performed by suspending the crystalline carvedilol in a solution mixture of ethyl acetate:water (150:40).

Optionally, the heating step may be performed by heating the solution mixture from about 60 to about 70° C. with agitation until the crystalline carvedilol is completely dissolved.

Optionally, the cooling step may be performed by cooling the solution mixture to about to 10° C. for a period of about 3 hours with agitation.

Formation of Crystalline Carvedilol Form IV

The present invention also provides a method for preparing crystalline carvedilol Form IV by forming a solvent solution containing carvedilol and inducing precipitation of crystalline carvedilol Form IV by the addition of an "anti-solvent". In this embodiment, solvents are optionally selected from the group which includes methyl ethyl ketone, and methyl isobutyl ketone. Anti-solvents are optionally selected from the group which includes cylcohexane and heptane.

Optionally, to form crystalline carvedilol Form IV carvedilol may be dissolved in a solvent at from below ambient temperature to elevated temperatures. The preferred temperature is from about 10° to about 50° C. Most preferably the temperature is ambient temperature.

Formation of Crystalline Carvedilol Form V

The present invention also provides a method for preparing crystalline carvedilol Form V by forming a solvent solution containing carvedilol and inducing precipitation of crystalline carvedilol solvate Form V by cooling or by adding an anti-solvent. In this embodiment, the solvent is optionally selected from the group which includes methyl ethyl ketone. Anti-solvents are optionally selected from the group which includes cylcohexane and hexane.

Optionally, to form crystalline carvedilol Form V the carvedilol may be dissolved in a solvent solution at elevated temperature. The preferred elevated temperature is from about 10 to about 80° C. Most preferably the elevated temperature is about 55° C. Alternatively, carvedilol may be dissolved in a solvent solution at ambient temperature.

Novel Hydrate and Solvate Crystal Forms of Carvedilol

The present invention provides novel crystal forms of carvedilol which will be designated as Forms III, IV and V, as well as carvedilol HCl. These forms can be distinguished from the prior art forms of carvedilol and from each other by characteristic powder X-ray diffraction patterns and thermal profiles.

The different crystal forms may also be characterized by their respective solvation state. The most commonly encountered solvates among pharmaceuticals are those of 1:1 stoichiometry. Occasionally mixed solvate species are encountered. When water or solvent is incorporated into the crystal lattice of a compound in stoichiometric proportions, the molecular adduct or adducts formed are referred to as hydrates or solvates.

Crystalline Carvedilol Form III

Carvedilol Form III ("Form III") is characterized by an X-ray diffraction pattern with peaks at about 8.4±0.2, 9.3±0.2, 11.6±0.2, 13.2±0.2, 13.5±0.2, 14.2±0.2, 15.3±0.2, 15.8±0.2, 17.4±0.2, 18.4±0.2, 19.4±0.2, 20.6±0.2, 21.4±0.2, 22.0±0.2, 26.6±0.2 and 27.6±0.2 degrees two-theta. The most characteristic peaks of Form III are at about 8.4±0.2, 17.4±0.2, and 22.0±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 1.

The DTG thermal profile of Form IV is shown in FIG. 2. The differential scanning calorimetry (DSC) thermal profile of form III shows one melting peak around 100° C. (96° C.–110° C.), depending on the samples and on the particle size. This melting peak is concomitant to a loss on drying of about 2% as measured by thermal gravimetric analysis (TGA). The amount of water in the sample as determined by Karl Fisher analysis is in good agreement with the value obtained from TGA, thus confirming that the loss on drying is due to the dehydration of water, and indicating that this material is a.

Crystalline Carvedilol Form IV

Carvedilol Form IV ("Form IV") is characterized by an X-ray diffraction pattern with peaks at about 11.9±0.2, 14.2±0.2, 15.7±0.2, 16.5±0.2, 17.7±0.2, 18.3±0.2, 19.2±0.2, 19.6±0.2, 21.7±0.2, 22.2±0.2, 23.9±0.2, 24.2±0.2, 24.9±0.2, 27.4±0.2 and 28.2±0.2 degrees two-theta. The most characteristic peaks of Form IV are at about 11.9±0.2, 14.2±0.2, 18.3±0.2, 19.2±0.2, 21.7±0.2, and 24.2±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 3.

The DTG thermal profile of Form IV is shown in FIG. 4. The DSC thermal profile of form IV shows one melting peak at about 104° C.

Crystalline Carvedilol Form V

Carvedilol Form V ("Form V") is characterized by an X-ray diffraction pattern with peaks at about 4.1±0.2, 10.3±0.2, 10.7±0.2, 11.5±0.2, 12.6±0.2, 14.0±0.2, 14.8±0.2, 15.4±0.2, 16.4±0.2, 16.8±0.2, 18.8±0.2, 20.8±0.2, 21.1±0.2, 21.6±0.2, and 25.4±0.2, degrees two-theta. The most characteristic peaks of Form IV are at about 4.1±0.2, 10.3±0.2, 10.7±0.2 and 11.5±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 5.

The DTG thermal profile of Form V is shown in FIG. 6. The DSC thermal profile of Form V shows a solvent desorption endotherm. at about 67° C., followed by a recrystallization event, and a melting peak at 115° C. The desorption endotherm is concomitant to a loss on drying of about 14% as determined by TGA. This behavior is consistent with the loss of a molecule of MEK per molecule of carvedilol (the calculated stoichiometric value of mono-MEK is 15%).

Carvedilol HCl Hydrate

Crystalline Carvedilol HCl is characterized by an X-ray diffraction pattern with peaks at about 6.5±0.2, 10.2±0.2,

10.4±0.2, 14.2±0.2, 14.7±0.2, 15.8±0.2, 16.4±0.2, 17.7±0.2, 20.0±0.2, 21.5±0.2, 21.9±0.2, 22.2±0.2, 22.9±0.2, 25.2±0.2, 25.3±0.2, 27.2±0.2, 27.4±0.2, 28.2±0.2, 28.6±0.2, 29.6±0.2 degrees two theta. The most characteristic peaks of crystalline carvedilol HCl are at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2, 16.4±0.2 and 22.2±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 7.

The DTG thermal profile of carvedilol HCl shows two endothermic peaks. A peak at 118° C. is a dehydration peak. A second peak endothermic peak at 135° C. is due to melting of the sample. LOD for this sample is 3.5%. The Water content of this sample as measured by Karl-Fisher analysis is 3.7%. Thus the Karl-Fisher analysis is in agreement with LOD value, and confirm the presence of hydrate in this sample. The expected value for carvedilol HCl monohydrate is 3.9%

A Pharmaceutical Composition Containing Carvedilol

According to another aspect, the present invention relates to a pharmaceutical composition comprising one or more of the novel crystal forms of carvedilol disclosed herein and at least one pharmaceutically acceptable excipient. Such pharmaceutical compositions may be administered to a mammalian patient in a dosage form.

The dosage forms may contain one or more of the novel forms of carvedilol or, alternatively, may contain one or more of the novel forms of carvedilol as part of a composition. Whether administered in pure form or in a composition, the carvedilol form(s) may be in the form of a powder, granules, aggregates or any other solid form. The compositions of the present invention include compositions for tableting. Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The novel forms of carvedilol disclosed herein also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The most preferred route of administration of the carvedilol forms of the present invention is oral.

Capsule dosages will contain the solid composition within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

The currently marketed form of carvedilol is available as a 3.125 mg, a 6.25 mg, a 12.5 mg, and a 25 mg tablet which includes the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

The function and advantage of these and other embodiments of the present invention will be more fully understood from the examples below. The following examples are intended to illustrate the benefits of the present invention, but do not exemplify the full scope of the invention.

EXAMPLES

Example 1

Preparation of Carvedilol in Neat Conditions

2-(2-Methoxyphenoxy)ethylamine (III) (4.89 g) was heated to about 100° C., after which 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (3.31 g) was added portionwise. After approximately 20 minutes, the reaction mixture was cooled to about 70° C., after which water (25 ml) and ethyl acetate (15 ml) were added. The pH of the two-phase mixture was then adjusted to 5 with 2 N hydrochloric acid. The solid that formed, Carvedilol hydrochloride hydrate, is filtered, washed with water (20 ml) followed with ethylacetate (15 ml). The resulting material is reslurried in ethylacetate (50 ml) and water (20 ml) containing 5% Sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4° C. Precipitated carvedilol was isolated by filteration and crystallized from isopropanol.

Example 2

Preparation of Carvedilol in Neat Conditions

2-(2-Methoxyphenoxy)ethylamine (III) (4.89 g) was heated to about 100° C., after which 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (3.31 g) was added portionwise. After approximately 20 minutes, the reaction mixture was cooled to about 70° C., after which water (25 ml) and ethyl acetate (15 ml) were added. The pH of the two-phase mixture was then adjusted to 5 with 2 N hydrochloric acid. The solid that formed, Carvedilol hydrochloride hydrate, is filtered, washed with water (20 ml) followed with ethylacetate (15 ml).

The resulting material is reslurried in ethylacetate (50 ml) and water (20 ml) containing 5% Sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4° C. Precipitated carvedilol was isolated by filteration and crystallized from methanol.

Example 3

Process for Preparing Form I of Carvedilol

Crystalline carvedilol is prepared according to the procedure in Example 3. The crystalline material is then dried at

50–60° C. for 6 hours. The dried crystalline carvedilol (220 g carvedilol) is dissolved in 2200 ml Ehtyl Acetate. The ethyl acetate solution is heated with agitation to 77° C. until the solid is completly dissolved. The ethyl acetate solution was then cooled with agitation to about 50° C. in a time period of 15 min. The cooled solution was stirred for 48 hours. The solution was then cooled to 10° C. in 0.75 hours with agitation. After stirring the suspension for additional 24 hours, the product was filtered. Pure Crystalline carvedilol Form I (170 g) was obtained.

Example 4

Preparation of Crystalline Carvedilol Form II

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table I. Carvedilol is crystallized by forming a solution of carvidilol heated to reach a clear solution, usually close to the solvent boiling temperature. The solution is then cooled to ambient temperature and the precipitate is filtered to yield Carvedilol for II.

TABLE I

Solvent	Ratio of Solvent (ml):Carvedilol (g)
Methanol	11
Ethanol abs.	12
1-propanol	14
Isopropanol	13
n-Butanol	11
Ethylen glycol	13
Ethyl-acetate	10
Butyl Acetate	12
isobutyl methl ketone	12
Dichloromethane	12
Dichloroethane	25
Acetonitile	50
Acetone	25

Example 5

Preparation of Crystalline Carvedilol Form II by Filtration at −20° C.

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table II. Carvedilol is crystallized by forming a solution of carvidilol heated to about the solvent boiling temperature. The solution is then cooled to −20° C., the precipitate is filtered and dried to yield Carvedilol Form II.

TABLE II

Solvent	Ratio of Solvent (ml):Carvedilol (g) [Please Confirm Units]
Isoamylalcohol	50
Toluene	53
Xylene	51

Example 6

Preparation of Crystalline Carvedilol Form II in Solvent Mixtures

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the mixture of solvents listed in Table III. Carvedilol is crystallized by forming a solution of carvidilol heated to form a clear solution, usually close to the boiling temperature of the mixture of solvent. The solution is then cooled to ambient temperature and filtered. The crystals are collected by filtration and dried to yeld Carvedilol form II.

TABLE III

Solvent	Solvents ratio	Ratio Solvent (ml):Carvedilol (g) [Please Confirm Units]
Acetone:Cyclohexane	1:4.8	230
Chloroform:Cyclohexane	1:3	130
Dichloroethane:cyclohexane	1:2.5	142
Dichloromethane:Cyclohexane	1:1.7	90
Pyridine:Cyclohexane	1:3.5	45
Tetrahydrofurane:Cyclohexane	1:2.5	53
Dioxane:Cyclohexane	1:2.3	70
Acetone:Hexane	1:2	235
Chloroform:hexane	1:1.5	87
Dichloroethane:Hexane	1:1.2	89
Dichloromethane:hexane	1:1.6	90
Tetrahydrofuran:Hexane	1:3	49
Ethanol:Hexane	1:3.8	145

Example 7

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 45 mL of a mixture of 96% Ethanol and 4% water by heating the mixture under stirring in a 55° C. water bath. The solution was cooled and left at room temperature without stirring for about 14 hours, the crystals were filtered through a buchner funnel, rinsed twice with about 10 ml cold (4° C.) 96% ethanol, and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 8

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 195 mL mixture of water/methanol (in a ratio 1:3 respectively) by heating the mixture under stirring in 55° C. water bath. The solution cooled to ambient temperature and left at ambient temperature without stirring for about 15 h, the crystals were filtered through a buchner and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 9

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 39 mL pyridine by stirring at room temperature. 70 mL of water was then added dropwise until crystallization began. The solution was left at room temperature without stirring for about 80 h, then the crystals were filtered through a buchner and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield Carvedilol Form III.

Example 10

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 76 mL dioxane at room temperature, and 110 mL of water were added in portions of about 10 mL to the stirred solution. The resulting solution was left at room temperature without stirring for about 15 h, then the crystalline precipitate which had formed was filtered through a buchner funnel and dried in desiccator at room temperature (connected to air pump) until constant weight to yield Carvedilol Form III in a mixture with Carvedilol Form II.

Example 11

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 267 mL dioxane/water in the ratio 1:1.4 respectively by heating the mixture under stirring at 55° C. water bath. The resulting solution was left at room temperature without stirring for about 15 h then the crystals were filtered through a buchner funnel and dried in a desiccator (connected to air pump) until constant weight to yield Carvedilol Form III in a mixture with Carvedilol Form II.

Example 12

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 180 ml, Hexane/IPA in a ratio 1:1 by heating the mixture under stirring at 55° C. water bath. The solution was allowed to sit at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator (connected to air pump) at room temperature until constant weight to yield Carvedilol Form III.

Example 13

Process for Preparing Form III of Carvedilol

Carvedilol (40 g) was dissolved in 150 ml of ethanol and 40 ml water. The solution was heated with agitation to 60–70° C. until the solid material was completely dissolved. The solution is then cooled with agitation to 10° C. over a period of 3 hours. After stirring the suspension for an additional 2.75 hours, the product is filtered. Pure Carvedilol Form III (35 g) was obtained.

Example 14

Preparation of Crystalline Carvedilol Form IV

Carvedilol (1 g) was dissolved in 35 mL methyl ethyl ketone by stirring at room temperature, and 202 mL cyclohexane was added dropwise. The solution was left at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form IV.

Example 15

Preparation of Crystalline Carvedilol Form V

Carvedilol (1 g) was dissolved in 70 mL methyl ethyl ketone by stirring at room temperature, and 138 mL hexane were added dropwise. The solution was left at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form V.

Example 16

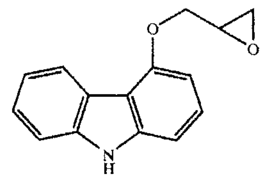
Preparation of Crystalline Carvedilol Form V

Carvedilol (2 g) was dissolved in 45 mL methyl ethyl ketone by heating the mixture under stirring at 55° C. water bath, then the solution was cooled and left at room temperature without stirring for about 14 hours, the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form V.

What is claimed is:

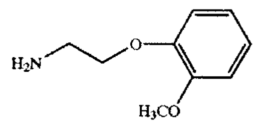
1. A process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,

II



with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine

III



wherein the compound of formula III and the compound of formula II are at a molar ratio of from about 2.8:1 to about 10:1.

2. The process of claim 1, wherein the compound of formula III and the compound of formula II are at a molar ratio from about 2.8:1 to about 6:1.

3. The process of claim 1, wherein the reacting step is performed in a solvent.

4. The process of claim 3, wherein the solvent is selected from the group consisting of toluene, xylene and heptane.

5. The process of claim 1, wherein the reacting step is performed in a solvent mixture wherein the solvent mixture comprises multiple solvents.

6. The process of claim 5, wherein a solvent of the solvent mixture is selected from the group consisting of toluene, xylene and heptane.

7. The process of claim 1, wherein the reacting step is performed at a temperature from about 25° C. to about 150° C.

8. The process of claim 1, wherein the reacting step is performed at a temperature from about 60° C. to about 120° C.

9. The process of claim 1, wherein the reacting step is performed under neat conditions.

10. The process of claim 9, wherein the neat conditions are obtained by melting a solid form of the compound of formula III to form a liquid and, dissolving the compound of formula II in the liquid to form a reaction mixture.

11. The process of claim 9, further comprising a step of reducing the temperature of the reaction mixture after dissolving the compound of formula II.

12. The process of claim 11, wherein the temperature is reduced to about 70° C.

13. The process of claim 9, further comprising a step of adding an organic solvent: water mixture to the reaction mixture.

14. The process of claim 13, wherein the organic solvent is selected from the group consisting of ethyl acetate, butyl acetate and methyl ethyl ketone.

15. The process of claim 13, further comprising a step of adjusting the pH of the organic solvent: water mixture to the reaction mixture after the organic solvent: water mixture is added to the reaction mixture.

16. The process of claim 15, wherein the pH is adjusted to less than about pH 5.

17. The process of claim 15, wherein the pH is adjusted from about pH 3 to about pH 5.

18. The process of claim **9**, further comprising steps of:

a) isolating carvedilol hydrochloride after adjusting the pH, and

b) purifying carvedilol.

19. The process of claim **18**, wherein carvedilol hydrochloride is a hydrate.

* * * * *

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Exhibit B

US007126008B2

(12) **United States Patent**
Hildesheim et al.

(10) **Patent No.: US 7,126,008 B2**
(45) **Date of Patent: *Oct. 24, 2006**

(54) **CARVEDILOL**

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(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/758,026**

(22) Filed: **Jan. 16, 2004**

(65) **Prior Publication Data**

US 2004/0225132 A1 Nov. 11, 2004

Related U.S. Application Data

(63) Continuation of application No. 09/894,798, filed on Jun. 28, 2001, now Pat. No. 6,699,997.

(51) **Int. Cl.**
C07D 209/82 (2006.01)

(52) **U.S. Cl.** **548/444**

(58) **Field of Classification Search** 548/444; 514/411

See application file for complete search history.

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Pharmacopeial Forum, vol. 24, No. 1, pp. 5438-5441, Jan.-Feb. 1998.

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*Chen, Wei-Min et al. "Synthesis and Crystal Structure of Carvedilol" Jiegou Huaxue, vol. 17, No. 5, Sep. 1998, pp. 325-328 (abstract included).

*Carey, Francis A. et al. "Advanced Organic Chemistry" Third Edition, Part A: Structure and Mechanisms; Plenum Press, pp. 232-239, 1993.

Primary Examiner—Kamal A. Saeed
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon LLP

(57) **ABSTRACT**

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof.

6 Claims, 7 Drawing Sheets

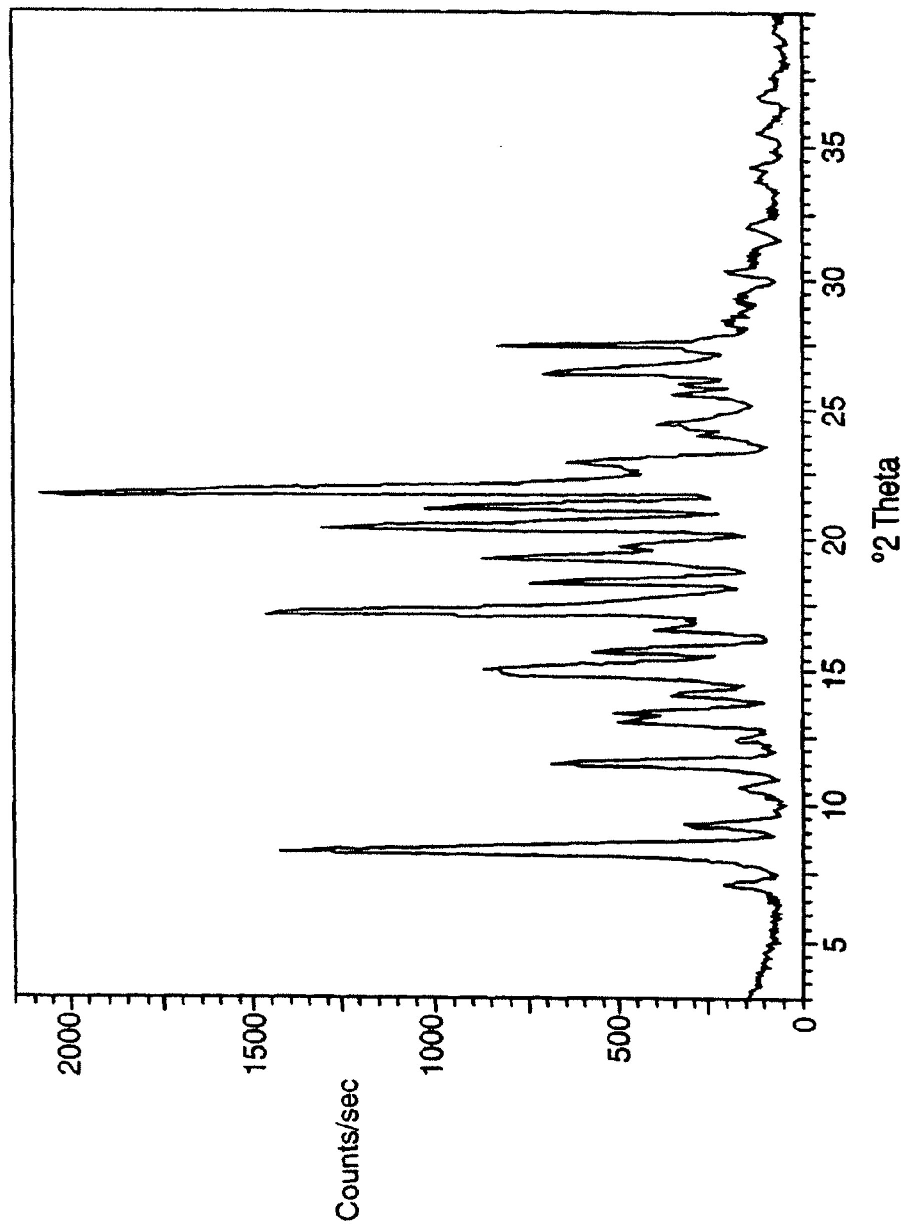

FIG. 1

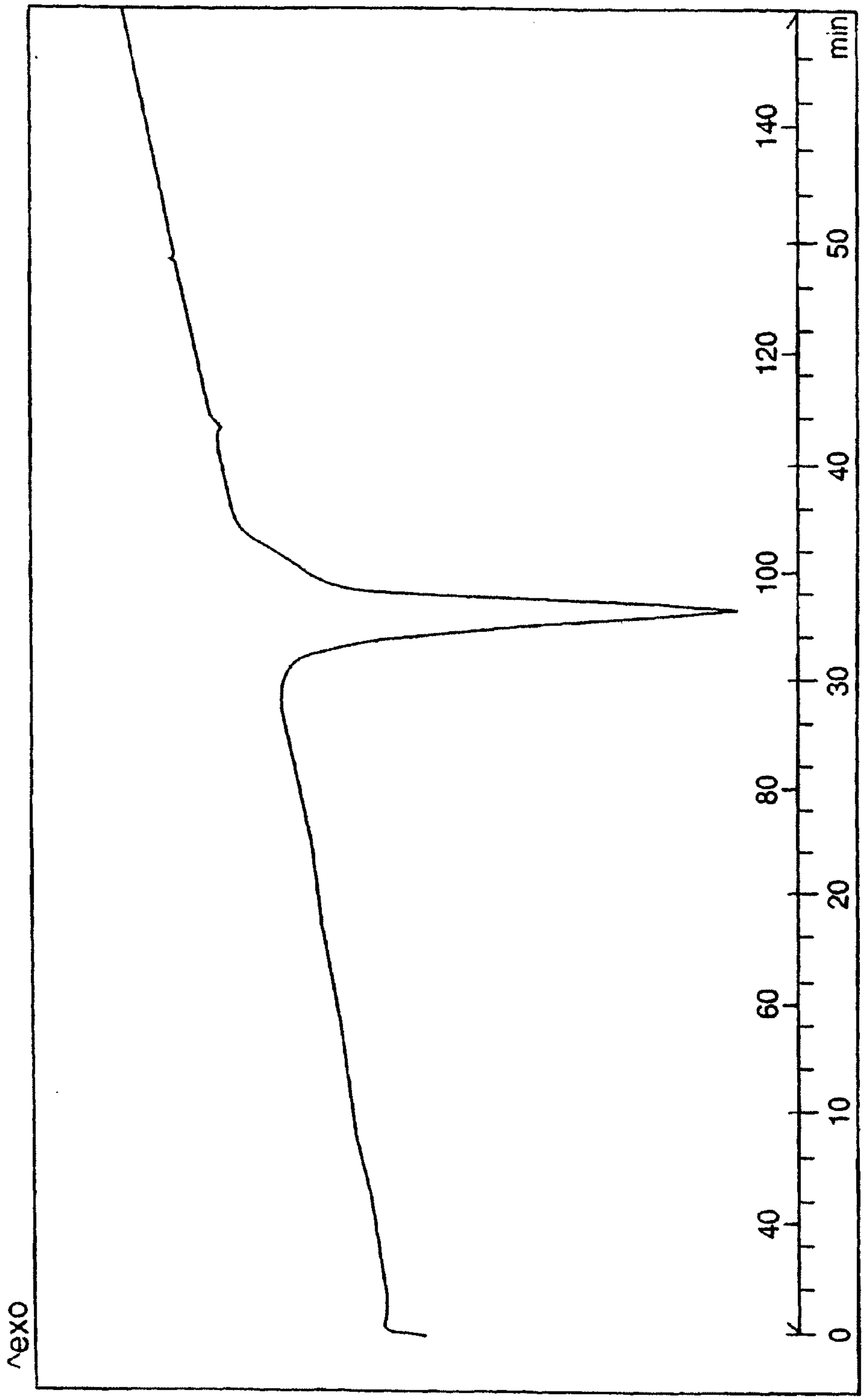

FIG. 2

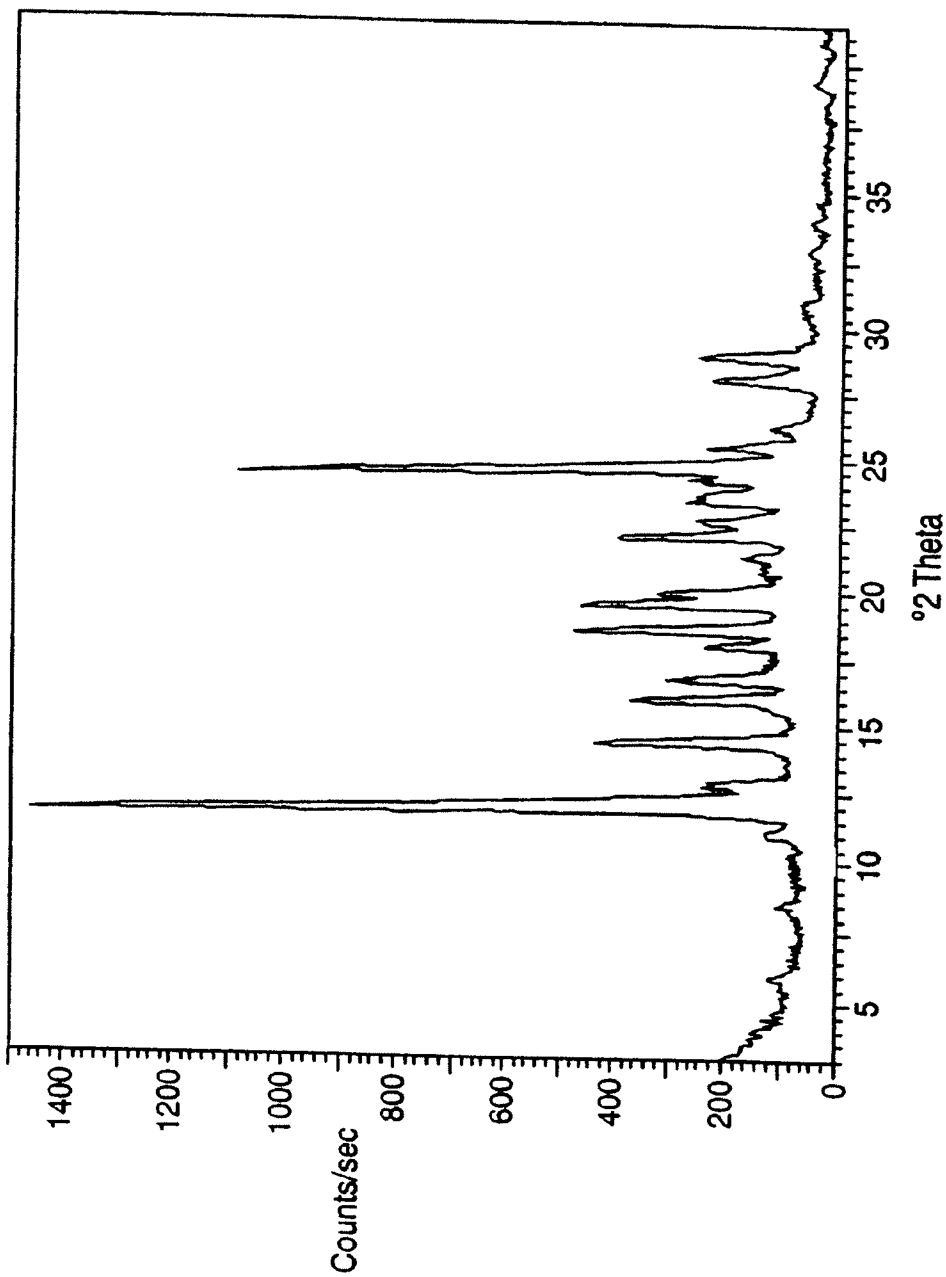
Counts/sec
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FIG. 3

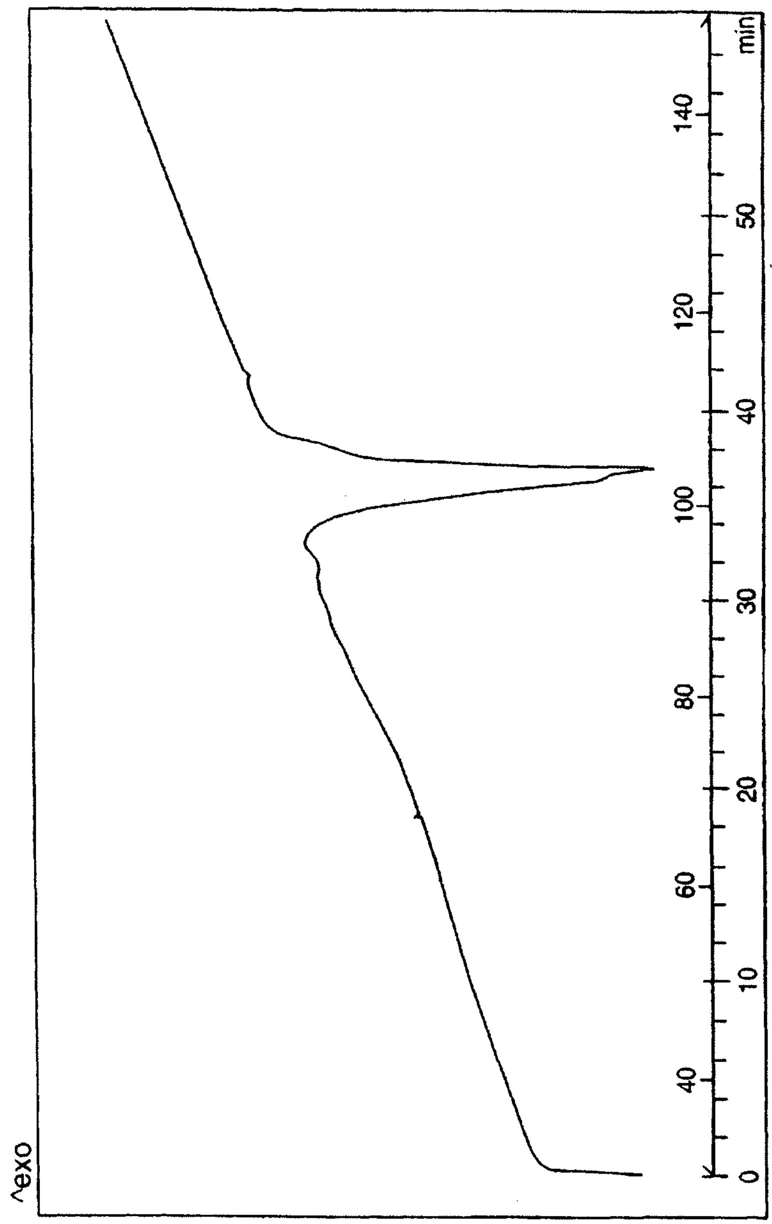

FIG. 4

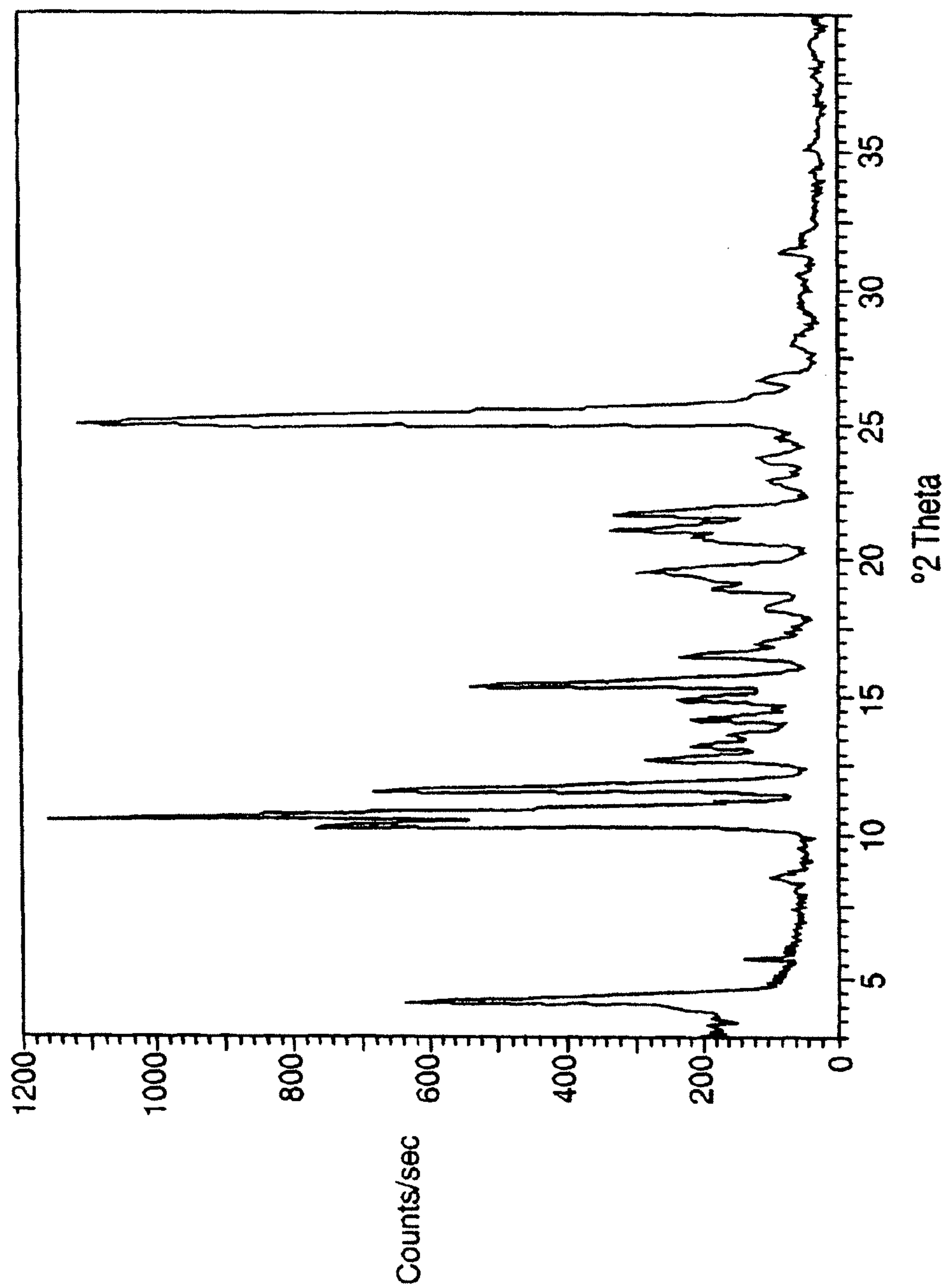

FIG. 5

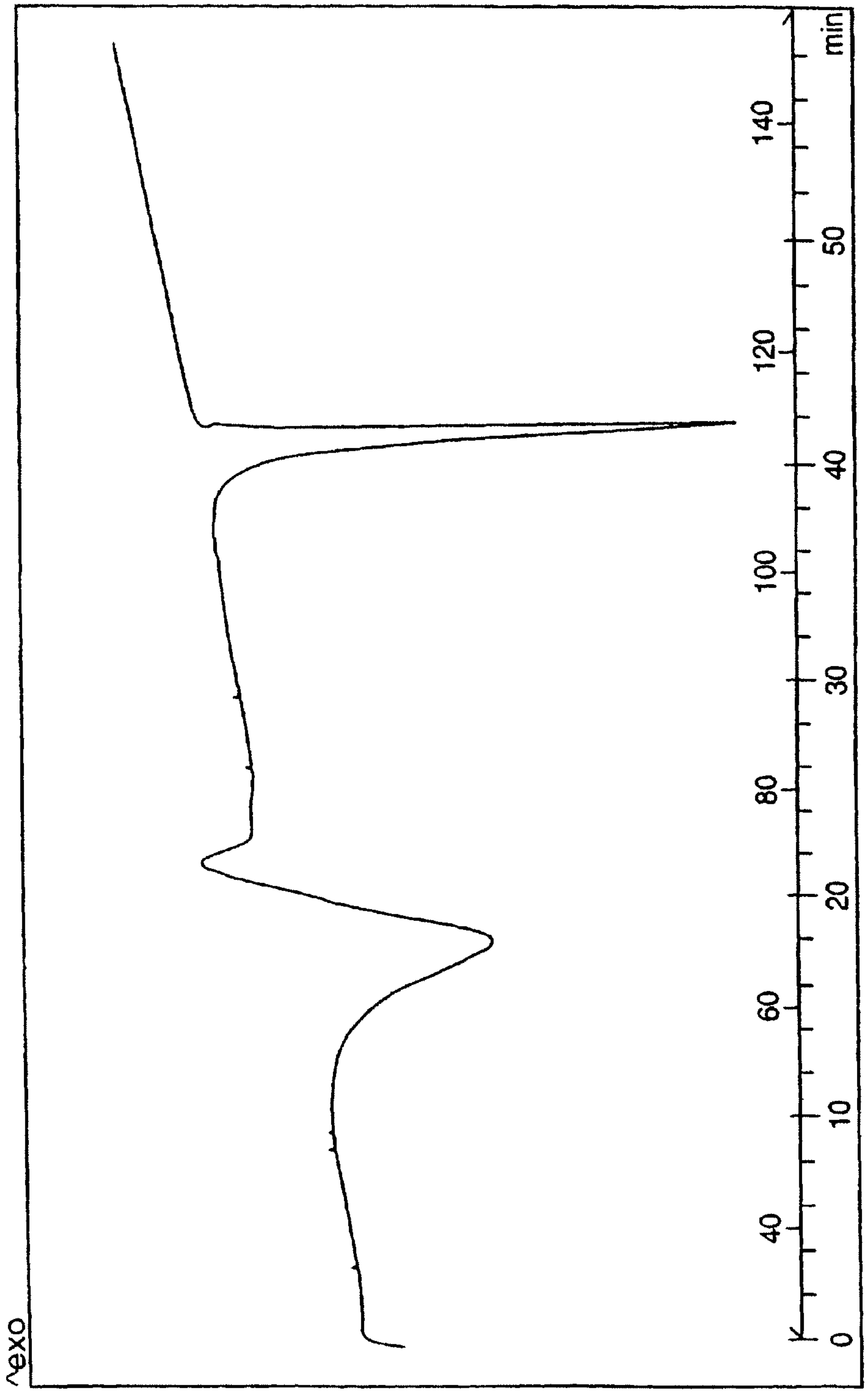

FIG. 6

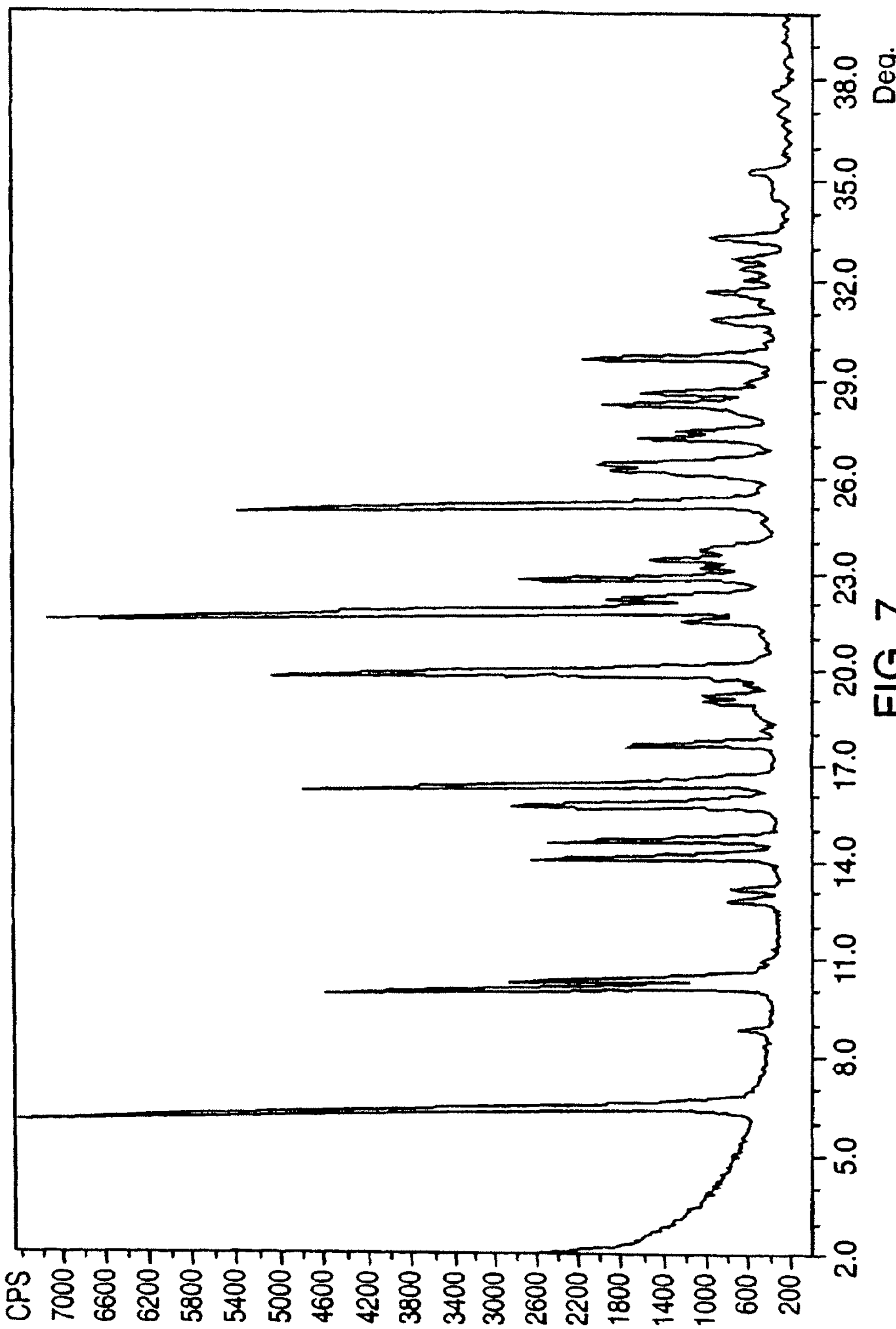
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FIG. 7

CARVEDILOL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of application Ser. No. 09/894,798 filed Jun. 28, 2001, now U.S. Pat. No. 6,699,997, and claims the benefit of U.S. provisional application Ser. No. 60/349,310, filed Jan. 15, 2002, which is incorporated herein by reference.

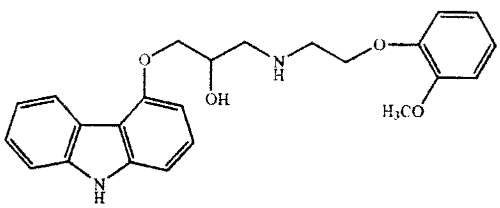
FIELD OF THE INVENTION

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1 blocking activity. Carvedilol, also known as (±) 1-(9H-carbazol-4-yloxy)-3-[[2(2-methoxyphenoxy)ethyl] amino]-2-propanol, (CAS Registry No. 72956-09-3) has the structure of formula I.

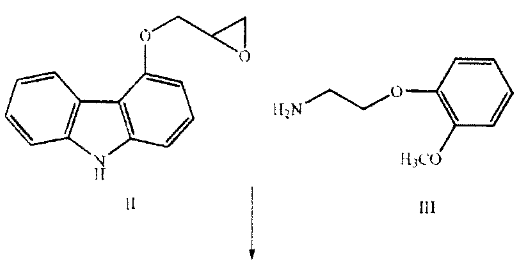
I



Carvedilol has a chiral center and can exist either as individual stereoisomers or in racemic form. Racemic carvedilol is the active ingredient of COREG®, which is indicated for the treatment of congestive heart failure and hypertension. The nonselective β-adrenergic activity of carvedilol is present in the S(−) enantiomer and the α_1 blocking activity is present in both the R(+) and S(−) enantiomers at equal potency. Both the racemate and stereoisomers may be obtained according to procedures well known in the art (EP B 0127 099).

Synthesis of Carvedilol

U.S. Pat. No. 4,503,067, which is incorporated herein by reference, discloses a process of preparing carvedilol by the following reaction:



II III

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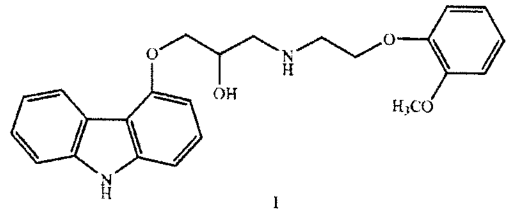
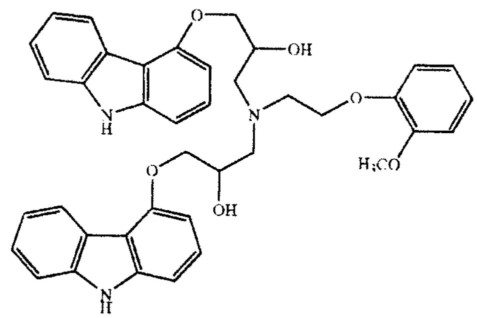


I

in which 4-(oxiran-2-ylmethoxy)-9H-carbazole (formula II) is reacted with (2-(2-methoxyphenoxy)ethylamine (formula III) to form carvedilol (I). The above process produces a low yield of carvedilol at least in part because in addition to carvedilol, the process leads to the production of a bis impurity of the following structure (formula IV):

IV



(See EP 918055.)

In order to reduce the formation of the formula IV and to increase the yield of carvedilol, EP 918055 discloses using a benzyl protected form of the 2-(2-methoxyphenoxy)ethylamine (III).

Carvedilol Polymorphs

International application No. WO 99/05105, incorporated herein by reference, discloses that carvedilol can be isolated as two polymorphic forms, depending on the method of preparation. The two polymorphic forms, designated Form I and Form II, are reported to be monotropic and are distinguishable by their infrared, Raman and X-ray powder diffraction spectra. No evidence is found in the literature about the existence of hydrated solvate states of carvedilol.

Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline form in the solid state. A single molecule may give rise to a variety of crystal forms (also called "polymorphs," "hydrates, " or "solvates") having distinct physical properties. [For a general review of polymorphs and the pharmaceutical applications of polymorphs see G. M. Wall, *Pharm Manuf.*, 3] For a general review of polymorphs and the pharmaceutical applications of polymorphs see *Pharm Manuf.*, 3, 33 (1986); J. K. Haleblian and W. McCrone, *J. Pharm. Sci.*, 58, 911(1969); and J. K. Haleblian, *J. Pharm. Sci.*, 64, 1269 (1975), all of which are incorporated herein by reference.

The existence and physical properties of different crystal forms can be determined by a variety of techniques such as

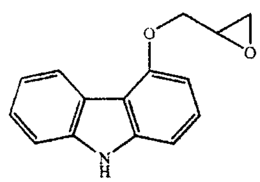
X-ray diffraction spectroscopy, differential scanning calorimetry and infrared spectroscopy. Differences in the physical properties of different crystal forms result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly, polymorphs, hydrates and solvates are distinct solids sharing the same molecular formula yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family. The existence and physical properties of polymorphs, hydrates and solvates is unpredictable.

One of the most important physical properties of a pharmaceutical compound which can form polymorphs, hydrates or solvates, is its solubility in aqueous solution, particularly the solubility in gastric juices of a patient. Other important properties relate to the ease of processing the form into pharmaceutical dosages, such as the tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet.

SUMMARY OF THE INVENTION

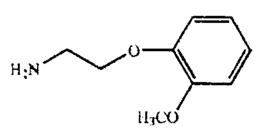
The present invention provides a process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,

II



with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine

III



wherein the compound of formula III is at a molar excess over the compound of formula II.

The present invention further provides crystalline carvedilol hydrate.

The present invention further provides crystalline carvedilol.

The present invention further provides crystalline carvedilol (methyl-ethyl-ketone) solvate.

The present invention further provides crystalline carvedilol Form III characterized by an X-ray powder diffraction pattern having peaks at about 8.4±0.2, 17.4±0.2, and 22.0±0.2 degrees two-theta.

The present invention further provides crystalline carvedilol Form IV characterized by an X-ray powder diffraction pattern having peaks at about 11.9±0.2, 14.2±0.2, 18.3±0.2, 19.2±0.2, 21.7±0.2, and 24.2±0.2 degrees two-theta.

The present invention further provides crystalline carvedilol (methyl-ethyl-ketone) solvate Form V characterized by an X-ray powder diffraction pattern having peaks at about 4.1±0.2, 10.3±0.2, and 10.7±0.2 degrees two-theta.

The present invention further provides carvedilol HCl Hydrate characterized by an X-ray powder diffraction pattern having peaks at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2, 16.4±0.2 and 22.2±0.2 degrees two-theta.

The present invention further provides a method for preparing crystalline carvedilol Form I, comprising the steps of dissolving carvedilol in a solution by heating; heating the solution until the crystalline carvedilol is completely dissolved; reducing the temperature of the solution; agitating the solution for a period of time; further reducing the temperature of the solution; further agitating the solution for a period of time; and collecting crystalline carvedilol Form I.

The present invention further provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent; precipitating carvedilol Form II by cooling the solution; and, isolating crystalline carvedilol Form II.

The present invention further provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent mixture; precipitating carvedilol Form II by cooling the solution to about −20° C.; and, isolating crystalline carvedilol Form II.

The present invention further provides a method for preparing crystalline carvedilol Form III, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating crystalline carvedilol Form III from the solvent solution using water as an anti-solvent.

The present invention further provides a method for preparing crystalline carvedilol Form III, comprising the steps of dissolving carvedilol in a solution by heating; cooling the solution mixture; and, collecting crystalline carvedilol Form III.

The present invention further provides a method for preparing crystalline carvedilol Form IV, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; adding an anti-solvent to the solvent solution; and, precipitating crystalline carvedilol Form IV from the solvent solution.

The present invention further provides a method for preparing crystalline carvedilol Form V, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating and isolating crystalline carvedilol Form V from the solvent solution.

The present invention further provides a method for preparing crystalline carvedilol Form V, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating and isolating crystalline carvedilol Form V from the solvent solution wherein the precipitation step is performed by adding an anti-solvent.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. shows the X-ray diffraction pattern of carvedilol Form III.

FIG. 2. shows the DTG thermal profile of carvedilol Form III.

FIG. 3. shows the X-ray diffraction pattern of carvedilol Form IV.

FIG. 4. shows the DTG thermal profile of carvedilol Form IV.

FIG. 5. shows the X-ray diffraction pattern of carvedilol Form V.

FIG. 6. shows the DTG thermal profile of carvedilol Form V.

FIG. 7. shows the X-ray diffraction pattern of carvedilol HCl.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "carvedilol" includes hydrates and solvates of carvedilol. The term "water content" refers to the content of water, based upon the Loss on Drying method (the "LOD" method) as described in Pharmacopeia Forum, Vol. 24, No. 1, p. 5438 (January-February 1998), the Karl Fisher assay for determining water content or thermogravimetric analysis (TGA). The term "equivalents of water" means molar equivalents of water. All percentages herein are by weight unless otherwise indicated. Those skilled in the art will also understand that the term "anhydrous", when used in reference to carvedilol, describes carvedilol which is substantially free of water. One skilled in the art will appreciate that the term "hemihydrate", when used in reference to carvedilol, describes a crystalline material having a water content of about 2.2% w/w. One skilled in the art will appreciate that the term "hydrate",in reference to carvedilol hydrochloride a crystalline material having a water content of about or above 2% w/w. One skilled in the art will also appreciate that the term "solvate of methyl-ethyl-ketone" refers to carvedilol in which solvent is contained within the crystal lattice in quantities above 1%. One skilled in the art will also appreciate that the term "solvate of methyl-ethyl-ketone" which contains one mole of is characterized by a methyl-ethyl-ketone content of about 14% by weight.

Hydrate and solvate forms of carvedilol are novel and distinct from each other in terms of their characteristic powder X-ray diffraction patterns and their thermal profiles.

For the purposes of this specification, ambient temperature is from about 20° C. to about 25° C.

All powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer. Copper radiation of $\lambda = 1.5418$ Å was used.

Measurement of thermal analysis are conducted for the purpose of evaluating the physical and chemical changes that may take place in a heated sample. Thermal reactions can be endothermic (e.g., melting, boiling, sublimation, vaporization, desolvation, solid-solid phase transitions, chemical degradation, etc.) or exothermic (e.g., crystallization, oxidative decomposition, etc.) in nature. Such methodology has gained widespread use in the pharmaceutical industry in characterization of polymorphism. Thermal measurements have proven to be useful in the characterization of polymorphic systems. The most commonly applied techniques are thermogravimetry (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC).

The DTA and TGA curves presented herein were obtained by methods known in the art using a DTG Shimadzu model DTG-50 (combined TGA and DTA). The weight of the samples was about 9 to about 13 mg. The samples were scanned up to about 300° C. or above at a rate of 10° C./min. Samples were purged with nitrogen gas at a flow rate of 20 ml/min. Standard alumina crucibles covered lids with one hole.

Thermogravimetry analysis (TGA) is a measure of the thermally induced weight loss of a material as a function of the applied temperature. TGA is restricted to transitions that involve either a gain or a loss of mass, and it is most commonly used to study desolvation processes and compound decomposition.

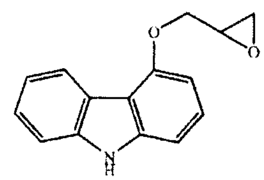
Karl Fisher analysis, which is well known in the art, is also used to determine the quantity of water in a sample.

As used herein, a solvent is any liquid substance capable of dissolving carvedilol. As used herein, the term "anti-solvent" means a liquid in which a compound is poorly soluble. The addition of an anti-solvent to a solvent reduces the solubility of a compound. As used herein a mixture of solvents refers to a composition comprising more than one solvent.

As used herein, the term "neat" conditions refers to conditions of a reaction wherein the solvent of the reaction is one of the reactants.

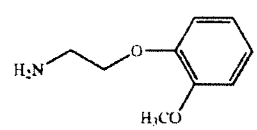
Synthesis of Carvedilol

According to one embodiment, the present invention is a process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,



II

with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine



III

The new procedure results in a higher yield of carvedilol than has been reported in the prior art. In addition, the product of the new procedure is nearly free of bis impurities and the reaction is more rapid.

Preferably, the compound of formula III is at a molar excess over the compound of formula II. The compound of formula III and the compound of formula II are preferably at a molar ratio from about 1.5:1 to about 100:1. More preferably, the compound of formula III and the compound of formula II are at a molar ration from about 2.8:1 to about 10:1. Most preferably, the compound of formula III and the compound of formula II are at a molar ratio from about 2.8:1 to about 6:1.

In one embodiment of the present invention, the reacting step is performed in a solvent. The solvent is preferably selected from the group consisting of toluene, xylene and heptane. In an alternative embodiment, the reacting step is performed in a solvent mixture wherein the solvent mixture comprises multiple solvents. Preferably, a solvent of the solvent mixture is selected from the group consisting of toluene, xylene and heptane.

The reacting step is preferably performed at a temperature from about 25° C. and about 150° C. Most preferably, the reacting step is performed at a temperature from about 60° C. and about 120° C.

In an alternative embodiment, the reacting step is performed under neat conditions. The neat conditions may obtained by melting a solid form of the compound of formula III to form a liquid and, dissolving the compound of formula II in the liquid to form a reaction mixture.

The reaction performed under neat conditions may further comprise a step of reducing the temperature of the reaction mixture after dissolving the compound of formula II. The temperature is preferably reduced to about 70° C.

The reaction performed under neat conditions may further comprise a step of adding an organic solvent: water mixture to the reaction mixture. The organic solvent is preferably selected from the group consisting of ethyl acetate, methyl isobutyl ketone, methyl ethyl ketone and butyl acetate.

The reaction performed under neat conditions may further comprise a step of adjusting the pH of the organic solvent: water mixture after it is added to the reaction mixture. The pH is preferably adjusted to less than about pH 5. More preferably, the pH is adjusted from about pH 3 to about pH 5.

Optionally, the process further comprises the steps of isolating carvedilol hydrochloride after adjusting the pH, and purifying carvedilol.

Carvedilol hydrochloride is optionally isolated as a hydrate. Carvedilol HCl isolated as a hydrate typically has an XRD peaks are found at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 14.2±0.2, 14.7±0.2, 16.4±0.2, 17.7±0.2, 20.0±0.2, 21.9±0.2, 25.2±0.2 degrees to 2-theta.

The reaction preformed under neat conditions may further comprise steps of, isolating carvedilol from the reaction mixture after adjusting the pH, and purifying carvedilol. Optionally, carvedilol may be purified by methods well known in the art. (See EP B 0127 099.)

Novel Methods for Preparing Crystalline Carvedilol Form I and Form II

One aspect of the present invention provides a method for preparing crystalline carvedilol Form I, by dissolving carvedilol in a solvent until the crystalline carvedilol is completely dissolved, reducing the temperature of the solution and agitating the solution for a period of time, further reducing the temperature of the solution and agitating the solution for a period of time and, collecting crystalline carvedilol Form I.

The dissolving step is optionally performed by heating the solvent.

The dissolving step is optionally performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

The dissolving step is optionally performed by suspending the crystalline carvedilol in ethyl acetate.

The dissolving step is optionally performed by heating the solution to about 77° C.

The step of reducing the temperature of the solution is optionally performed by cooling the solution to about 50° C. in a time period of 15 min.

The step of agitating solution is optionally performed at about 50° C. for about 48 hours.

The step of further reducing the temperature of the solution is optionally performed by cooling the solution to about 10° C. in about 0.75 hours with agitation.

The step of further agitating the solution is optionally performed by stirring the suspension for more than 5 hours.

The step of further agitation may optionally be performed by stirring the suspension for about 24 hours.

The drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

The suspending step may be performed by suspending the crystalline carvedilol in ethyl acetate.

The heating step may be performed by heating the solution to about 77° C.

Another aspect of the present invention provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent, precipitating carvedilol Form II by cooling the solution, and isolating crystalline carvedilol Form II.

Optionally, the step of dissolving carvedilol is performed at a temperature from about 40° C. to about the boiling temp of the solvent.

Optionally, the step of cooling the solution is performed by reducing the temperature from about −20° C. to about ambient temperature.

Optionally, the solvent is selected from the group consisting of methanol, absolute ethanol, 1-propanol, isopropanol, n-butanol, ethylene glycol, butyl acetate, isobutyl methyl ketone, dichloromethane, dichloroethane, acetonitrile, acetone, isoamylalcohol, xylene and toluene.

Optionally, the precipitated carvedilol Form II is isolated by filtration.

Another aspect of the present invention provides a method for preparing crystalline carvedilol Form II, comprising the steps of: forming a solution of carvedilol by dissolving carvedilol in a solvent mixture, precipitating carvedilol Form II by cooling the solution to about −20° C., and isolating crystalline carvedilol Form II.

Optionally, the carvedilol is dissolved in a solution at a temperature from about 40° C. to about the boiling temperature of the solvent.

Optionally, the carvedilol Form II is isolated by filtration.

Optionally, the step of cooling the reaction is performed by cooling the solution to a temperature from about −20° C. to ambient temperature.

Optionally, the solvent mixture is selected from the group consisting of acetone:cyclohexane, chloroform:cyclohexane, dichioroethane:cyclohexane, dichioromethane:cyclohexane, pyridine:cyclohexane, tetrahydrofuran:cyclohexane, dioxane:cyclohexane, acetone:hexane, chloroform:hexane, dichioroethane:hexane, dichioromethane:hexane, tetrahydrofuran:hexane and ethanol:hexane.

Novel Carvedilol Polymorphs

In another aspect the present invention provides new crystalline forms of carvedilol, designated Forms III, IV, V and processes for the manufacture thereof. Moreover, the present invention provides a new hydrate form of carvedilol, having water content of about 2% by weight and processes for their manufacture. In another embodiment, the present invention provides new solvate forms of carvedilol, having solvent content up to about 14% by weight, wherein the solvent is methyl ethyl ketone, and processes for their manufacture. These hydrate/solvate forms of carvedilol are useful as intermediates for the synthesis of carvedilol drug substances.

Procedures for Crystallizing Novel Forms of Carvedilol

The novel hydrates/solvates forms provided herein are optionally formed by precipitating carvedilol as a crystalline solid from a solvent or a solvent mixture. It will be understood by those of skill in the art, that other methods may also

be used to form the hydrate/solvates form disclosed herein. Alternatively the polymorphs may be formed by routine modification of the procedures disclosed herein.

Formation of Crystalline Carvedilol Form III.

One embodiment of the present invention provides a method for preparing crystalline carvedilol Form III, which comprises the steps of forming a solvent solution containing carvedilol; and, precipitating crystalline carvedilol Form III from the solvent solution using water as an anti-solvent. The invention provides for a dissolving step wherein water is present in the solvent solution during the dissolving step. The invention also provides for a precipitation step wherein water is added to the solution after carvedilol is fully dissolved in a solvent.

Optionally, to form the solvent solution containing carvedilol, carvedilol may be dissolved in a solvent at elevated temperature. The preferred elevated temperature is from about 40 to about 90° C. Most preferably the elevated temperature is about 55° C. Alternatively, carvedilol may be dissolved in a solvent at ambient temperature.

Another embodiment of the present invention provides, forming the solvent solution containing carvedilol, by dissolving carvedilol in a solvent and inducing precipitation of crystalline carvedilol Form III by the addition of an anti-solvent. Solvents are optionally selected from the group which includes pyridine, dioxane, isopropanol and chloroform. Anti-solvents are optionally selected from the group which includes water and hexane.

An alternative embodiment of the present invention provides, forming the solvent solution containing carvedilol by dissolving carvedilol in an organic solvent and water and precipitating crystalline carvedilol Form III. In this embodiment the organic solvent is optionally an alcohol. The alcohol is preferably selected from the group consisting of methanol and ethanol. Alternatively, the organic solvent may be selected from the group of solvents consisting of pyridine, dioxane, and ethyl acetate and tetrahydrofuran.

An alternative embodiment of the present invention provides, a method for preparing crystalline carvedilol Form III, comprising the steps of: drying crystalline carvedilol at elevated temperature, suspending crystalline carvedilol in a solution mixture, heating the solution mixture until the crystalline carvedilol is completely dissolved, cooling the solution mixture, and collecting crystalline carvedilol Form III.

Optionally, the drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

Optionally, the suspending step may be performed by suspending the crystalline carvedilol in a solution mixture of ethyl acetate:water (150:40).

Optionally, the heating step may be performed by heating the solution mixture from about 60 to about 70° C. with agitation until the crystalline carvedilol is completely dissolved.

Optionally, the cooling step may be performed by cooling the solution mixture to about to 10° C. for a period of about 3 hours with agitation.

Formation of Crystalline Carvedilol Form IV.

The present invention also provides a method for preparing crystalline carvedilol Form IV by forming a solvent solution containing carvedilol and inducing precipitation of crystalline carvedilol Form IV by the addition of an "anti-solvent". In this embodiment, solvents are optionally selected from the group which includes methyl ethyl ketone, and methyl isobutyl ketone. Anti-solvents are optionally selected from the group which includes cylcohexane and heptane.

Optionally, to form crystalline carvedilol Form IV carvedilol may be dissolved in a solvent at from below ambient temperature to elevated temperatures. The preferred temperature is from about 10° to about 50° C. Most preferably the temperature is ambient temperature.

Formation of Crystalline Carvedilol Form V.

The present invention also provides a method for preparing crystalline carvedilol Form V by forming a solvent solution containing carvedilol and inducing precipitation of crystalline carvedilol solvate Form V by cooling or by adding an anti-solvent. In this embodiment, the solvent is optionally selected from the group which includes methyl ethyl ketone. Anti-solvents are optionally selected from the group which includes cylcohexane and hexane.

Optionally, to form crystalline carvedilol Form V the carvedilol may be dissolved in a solvent solution at elevated temperature. The preferred elevated temperature is from about 10 to about 80° C. Most preferably the elevated temperature is about 55° C. Alternatively, carvedilol may be dissolved in a solvent solution at ambient temperature.

Novel Hydrate and Solvate Crystal Forms of Carvedilol

The present invention provides novel crystal forms of carvedilol which will be designated as Forms III, IV and V, as well as carvedilol HCl. These forms can be distinguished from the prior art forms of carvedilol and from each other by characteristic powder X-ray diffraction patterns and thermal profiles.

The different crystal forms may also be characterized by their respective solvation state. The most commonly encountered solvates among pharmaceuticals are those of 1:1 stoichiometry. Occasionally mixed solvate species are encountered. When water or solvent is incorporated into the crystal lattice of a compound in stoichiometric proportions, the molecular adduct or adducts formed are referred to as hydrates or solvates.

Crystalline Carvedilol Form III

Carvedilol Form III ("Form III") is characterized by an X-ray diffraction pattern with peaks at about 8.4±0.2, 9.3±0.2, 11.6±0.2, 13.2±0.2, 13.5±0.2, 14.2±0.2, 15.3±0.2, 15.8±0.2, 17.4±0.2, 18.4±0.2, 19.4±0.2, 20.6±0.2, 21.4±0.2, 22.0±0.2, 26.5±0.2 and 27.6±0.2 degrees two-theta. The most characteristic peaks of Form III are at about 8.4±0.2, 17.4±0.2, and 22.0±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 1.

The DTG thermal profile of Form IV is shown in FIG. 2. The differential scanning calorimetry (DSC) thermal profile of Form III shows one melting peak around 100°_C. (96°_C.–110°_C.), depending on the samples and on the particle size. This melting peak is concomitant to a loss on drying of about 2% as measured by thermal gravimetric analysis (TGA). The amount of water in the sample as determined by Karl Fisher analysis is in good agreement with the value obtained from TGA, thus confirming that the loss on drying is due to the dehydration of water, and indicating that this material is a hemihydrate.

Crystalline Carvedilol Form IV

Carvedilol Form IV ("Form IV") is characterized by an X-ray diffraction pattern with peaks at about 11.9±0.2, 14.2±0.2, 15.7±0.2, 16.5±0.2, 17.7±0.2, 18.3±0.2, 19.2±0.2, 19.6±0.2, 21.7±0.2, 22.2±0.2, 23.9±0.2, 24.2±0.2, 24.9±0.2, 27.4±0.2 and 28.2±0.2 degrees two-theta. The most characteristic peaks of Form IV are at about 11.9±0.2, 14.2±0.2,

18.3±0.2, 19.2±0.2, 21.7±0.2, and 24.2±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. **3**.

The DTG thermal profile of Form IV is shown in FIG. **4**. The DSC thermal profile of Form IV shows one melting peak at about 104°_C.

Crystalline Carvedilol Form V

Carvedilol Form V ("Form V") is characterized by an X-ray diffraction pattern with peaks at about 4.1±0.2, 10.3±0.2, 10.7±0.2, 11.5±0.2, 12.6±0.2, 14.0±0.2, 14.8±0.2, 15.4±0.2, 16.4±0.2, 16.8±0.2, 18.8±0.2, 20.8±0.2, 21.1±0.2, 21.6±0.2, and 25.4±0.2, degrees two-theta. The most characteristic peaks of Form IV are at about 4.1±0.2, 10.3±0.2, 10.7±0.2 and 11.5±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. **5**.

The DTG thermal profile of Form V is shown in FIG. **6**. The DSC thermal profile of Form V shows a solvent desorption endotherm at about 67°_C., followed by a recrystallization event, and a melting peak at 115°_C. The desorption endotherm is concomitant to a loss on drying of about 14% as determined by TGA. This behavior is consistent with the loss of a molecule of MEK per molecule of carvedilol (the calculated stoichiometric value of mono-MEK is 15%).

Carvedilol HCl Hydrate

Crystalline Carvedilol HCl is characterized by an X-ray diffraction pattern with peaks at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 14.2±0.2, 14.7±0.2, 15.8±0.2, 16.4±0.2, 17.7±0.2, 20.0±0.2, 21.5±0.2, 21.9±0.2, 22.2±0.2, 22.9±0.2, 25.2±0.2, 25.3±0.2, 27.2±0.2, 27.4±0.2, 28.2±0.2, 28.6±0.2, 29.6±0.2 degrees two theta. The most characteristic peaks of crystalline carvedilol HCl are at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2,16.4±0.2 and 22.2±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. **7**.

The DTG thermal profile of carvedilol HCl shows two endothermic peaks. A peak at 118° C. is a dehydration peak. A second peak endothermic peak at 135° C. is due to melting of the sample. LOD for this sample is 3.5%. The Water content of this sample as measured by Karl-Fisher analysis is 3.7%. Thus the Karl-Fisher analysis is in agreement with LOD value, and confirm the presence of hydrate in this sample. The expected value for carvedilol HCl monohydrate is 3.9%

A Pharmaceutical Composition Containing Carvedilol

According to another aspect, the present invention relates to a pharmaceutical composition comprising one or more of the novel crystal forms of carvedilol disclosed herein and at least one pharmaceutically acceptable excipient. Such pharmaceutical compositions may be administered to a mammalian patient in a dosage form.

The dosage forms may contain one or more of the novel forms of carvedilol or, alternatively, may contain one or more of the novel forms of carvedilol as part of a composition. Whether administered in pure form or in a composition, the carvedilol form(s) may be in the form of a powder, granules, aggregates or any other solid form. The compositions of the present invention include compositions for tableting. Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted cellulo-

ses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The novel forms of carvedilol disclosed herein also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The most preferred route of administration of the carvedilol forms of the present invention is oral.

Capsule dosages will contain the solid composition within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

The currently marketed form of carvedilol is available as a 3.125 mg, a 6.25 mg, a 12.5 mg, and a 25 mg tablet which includes the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

The function and advantage of these and other embodiments of the present invention will be more fully understood from the examples below. The following examples are intended to illustrate the benefits of the present invention, but do not exemplify the full scope of the invention.

EXAMPLES

Example 1

Preparation of Carvedilol in Neat Conditions.

2-(2-Methoxyphenoxy)ethylamine (III) (4.89 g) was heated to about 100° C., after which 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (3.31 g) was added portionwise. After approximately 20 minutes, the reaction mixture was cooled to about 70° C., after which water (25 ml) and ethyl acetate (15 ml) were added. The pH of the two-phase mixture was then adjusted to 5 with 2 N hydrochloric acid. The solid that formed, Carvedilol hydrochloride hydrate, is filtered, washed with water (20 ml) followed with ethyl acetate (15 ml).

The resulting material is reslurried in ethylacetate (50mL) and water (20mL) containing 5% sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4°_C. Precipitated carvedilol was isolated by filtration and crystallized from isopropanol.

Example 2

Preparation of Carvedilol in Neat Conditions.

2-(2-Methoxyphenoxy)ethylamine (III) (4.89 g) was heated to about 100° C., after which 4-(oxiran-2-yl-methoxy)-9H-carbazole (II) (3.31 g) was added portionwise. After approximately 20 minutes, the reaction mixture was cooled to about 70° C., after which water (25 ml) and ethyl acetate (15 ml) were added. The pH of the two-phase mixture was then adjusted to 5 with 2 N hydrochloric acid. The solid that formed, Carvedilol hydrochloride hydrate, is filtered, washed with water (20 ml) followed with ethyl acetate (15 ml).

The resulting material is reslurried in ethyl_acetate (50mL) and water (20mL) containing 5% sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4°_C. Precipitated carvedilol was isolated by filtration and crystallized from methanol.

Example 3

Process for Preparing Form I of Carvedilol

The dried crystalline carvedilol (220 g carvedilol) is dissolved in 2200 mL ethyl acetate. The ethyl acetate solution is heated with agitation to 77°_C. until the solid is completely dissolved. The ethyl acetate solution was then cooled with agitation to about 50°_C. in atime period of 15 minutes. The cooled solution was stirred for 48 hours. The solution was then cooled to 10°_C. in 0.75 hours with agitation. After stirring the suspension for additional 24 hours, the product was filtered. Pure Crystalline carvedilol Form I (170 g) was obtained.

Example 4

Preparation of Crystalline Carvedilol Form II.

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table I. Carvedilol is crystallized by forming a solution of carvedilol heated to reach a clear solution, usually close to the solvent boiling temperature. The solution is then cooled to ambient temperature and the precipitate is filtered to yield carvedilol Form II.

TABLE I

Solvent	Ratio of Solvent (mL):Carvedilol (g)
Methanol	11
Ethanol abs.	12
1-Propanol	14
Isopropanol	13
n-Butanol	11
Ethylen Glycol	13
Ethyl-Acetate	10
Butyl Acetate	12
Isobutyl Methl	12

TABLE I-continued

Solvent	Ratio of Solvent (mL):Carvedilol (g)
Ketone	
Dichloromethane	12
Dichloroethane	25
Acetonitile	50
Acetone	25

Example 5

Preparation of Crystalline Carvedilol Form II by Filtration at −20° C.

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table II. Carvedilol is crystallized by forming a solution of carvedilol heated to about the solvent boiling temperature. The solution is then cooled to −20°_C., the precipitate is filtered and dried to yield carvedilol Form II.

TABLE II

Solvent	Ratio of Solvent (mL):Carvedilol (g)
Isoamylalcohol	50
Toluene	53
Xylene	51

Example 6

Preparation of Crystalline Carvedilol Form II in Solvent Mixtures

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the mixture of solvents listed in Table III. Carvedilol is crystallized by forming a solution of carvedilol heated to form a clear solution, usually close to the boiling temperature of the mixture of solvent. The solution is then cooled to ambient temperature and filtered. The crystals are collected by filtration and dried to yield carvedilol Form II.

TABLE III

Solvent	Solvents ratio	Ratio Solvent (ml):Carvedilol (g) [Please Confirm Units]
Acetone:Cyclohexane	1:4.8	230
Chloroform:Cyclohexane	1:3	130
Dichloroethane:cyclohexane	1:2.5	142
Dichloromethane:Cyclohexane	1:1.7	90
Pyridine:Cyclohexane	1:3.5	45
Tetrahydrofurane:Cyclohexane	1:2.5	53
Dioxane:Cyclohexane	1:2.3	70
Acetone:Hexane	1:2	235
Chloroform:hexane	1:1.5	87
Dichloroethane:Hexane	1:1.2	89
Dichloromethane:hexane	1:1.6	90
Tetrahydrofuran:Hexane	1:3	49
Ethanol:Hexane	1:3.8	145

Example 7

Preparation of Crystalline Carvedilol Form III.

Carvedilol (4 g) was dissolved in 45 ml. of a mixture of 96% Ethanol and 4% water by heating the mixture under

stirring in a 55° C. water bath. The solution was cooled and left at room temperature without stirring for about 14 hours, the crystals were filtered through a buchner funnel, rinsed twice with about 10 ml cold (4° C.) 96% ethanol, and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 8

Preparation of Crystalline Carvedilol Form III.

Carvedilol (4_g) was dissolved in 195_mL mixture of water/methanol (in a ratio 1:3 respectively) by heating the mixture under stirring in 55°_C. water bath. The solution cooled to ambient temperature and left at ambient temperature without stirring for about 15 hours, the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 9

Preparation of Crystalline Carvedilol Form III.

Carvedilol (4_g) was dissolved in 39_mL pyridine by stirring at room temperature. 70 mL of water was then added dropwise until crystallization began. The solution was left at room temperature without stirring for about 80 hours, then the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 10

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 76 mL dioxane at room temperature, and 110 mL of water were added in portions of about 10 mL to the stirred solution. The resulting solution was left at room temperature without stirring for about 15 h, then the crystalline precipitate which had formed was filtered through a buchner funnel and dried in desiccator at room temperature (connected to air pump) until constant weight to yield Carvedilol Form III in a mixture with Carvedilol Form II.

Example 11

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 267 mL dioxane/water in the ratio 1:1.4 respectively by heating the mixture under stirring at 55° C. water bath. The resulting solution was left at room temperature without stirring for about 15 h then the crystals were filtered through a buchner funnel and dried in a desiccator (connected to air pump) until constant weight to yield Carvedilol Form III in a mixture with Carvedilol Form II.

Example 12

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 180 ml. Hexane/IPA in a ratio 1:1 by heating the mixture under stirring at 55° C. water bath. The solution was allowed to sit at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator (connected to air pump) at room temperature until constant weight to yield Carvedilol Form III.

Example 13

Process for Preparing Form III of Carvedilol

Carvedilol (40 g) was dissolved in 150 ml of ethanol and 40 ml water. The solution was heated with agitation to 60–70° C. until the solid material was completely dissolved. The solution is then cooled with agitation to 10° C. over a period of 3 hours. After stirring the suspension for an additional 2.75 hours, the product is filtered. Pure Carvedilol Form III (35 g) was obtained.

Example 14

Preparation of Crystalline Carvedilol Form IV.

Carvedilol (1 g) was dissolved in 35 mL methyl ethyl ketone by stirring at room temperature, and 202 mL cyclohexane was added dropwise. The solution was left at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form IV.

Example 15

Preparation of Crystalline Carvedilol Form V.

Carvedilol (1 g) was dissolved in 70 mL methyl ethyl ketone by stirring at room temperature, and 138 mL hexane were added dropwise. The solution was left at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form V.

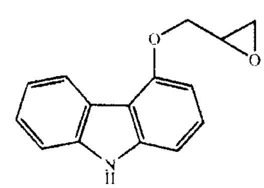
Example 16

Preparation of Crystalline Carvedilol Form V.

Carvedilol (2 g) was dissolved in 45 mL methyl ethyl ketone by heating the mixture under stirring at 55° C. water bath, then the solution was cooled and left at room temperature without stirring for about 14 hours, the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form V.

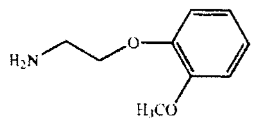
What is claimed is:

1. A process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,



II

with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine



III

wherein the compound of formula III is at a molar excess over the compound of formula II.

2. The process of claim **1**, wherein the compound of formula III and the compound of formula II are at a molar ratio from about 1.5:1 to about 100:1.

3. The process of claim **1**, wherein the reacting step is performed under neat conditions.

4. The process of claim **3**, wherein the neat conditions are obtained by melting a solid form of the compound of formula III to form a liquid and dissolving the compound of formula II in the liquid to form a reaction mixture.

5. The process of claim **2**, wherein the reacting step is performed under neat conditions.

6. The process of claim **5**, wherein the neat conditions are obtained by melting a solid form of the compound of formula III to form a liquid and dissolving the compound of formula II in the liquid to form a reaction mixture.

* * * * *

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Exhibit C

US006710184B2

(12) **United States Patent**
Kor et al.

(10) **Patent No.: US 6,710,184 B2**
(45) **Date of Patent: Mar. 23, 2004**

(54) **CRYSTALLINE SOLIDS OF CARVEDILOL AND PROCESSES FOR THEIR PREPARATION**

(75) Inventors: **Ilan Kor**, Shoham (IL); **Shlomit Wizel**, Petah Tiqva (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/342,905**

(22) Filed: **Jan. 15, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**^{7} **C07D 401/12**

(52) **U.S. Cl.** **548/444**

(58) **Field of Search** 548/444

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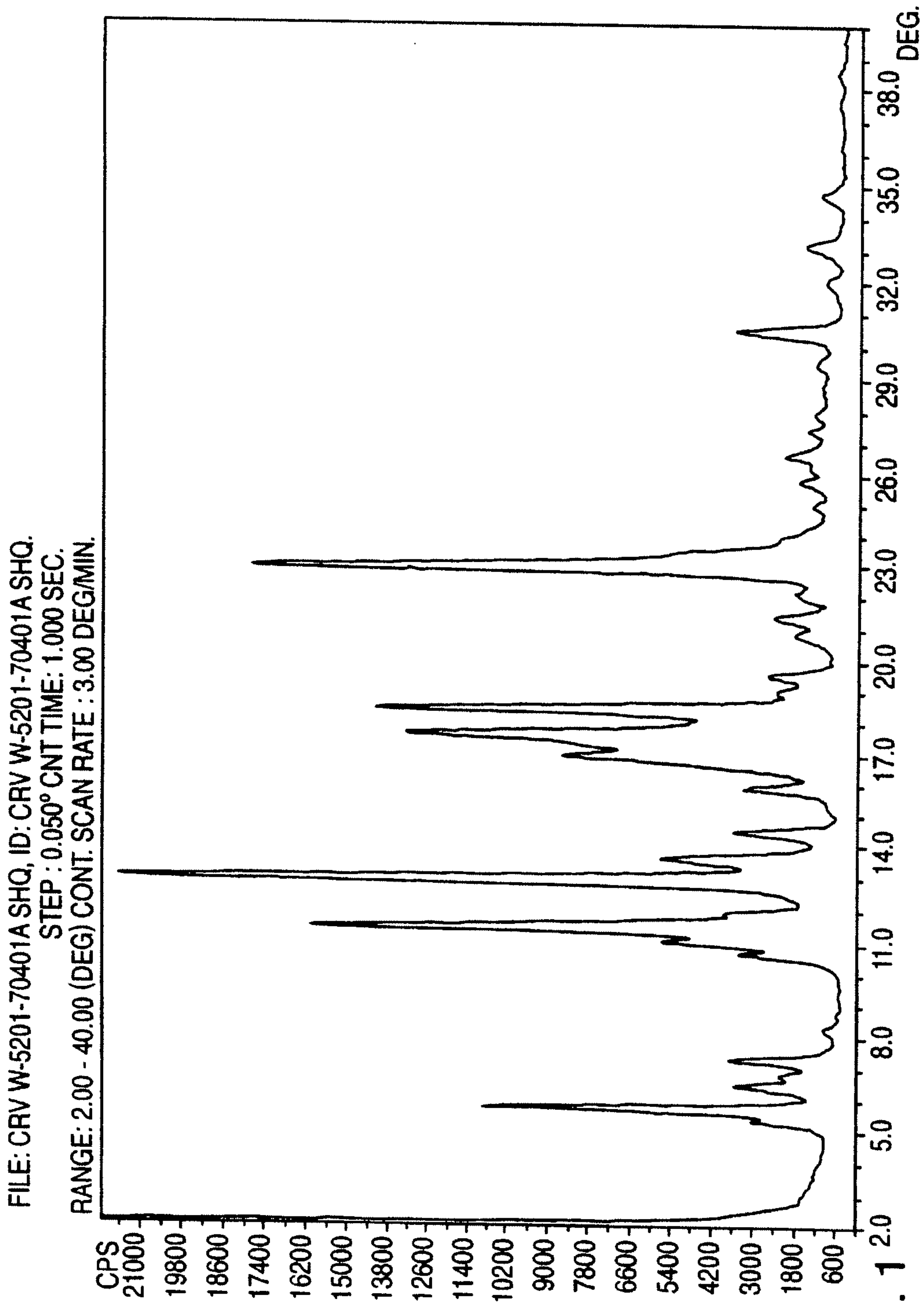
(57) **ABSTRACT**

This invention relates to a novel crystalline solid of carvedilol or a solvate thereof, to processes for its preparation, to compositions containing it and to its use in medicine. This invention further relates to a novel process for preparing a crystalline solid of carvedilol Form II.

4 Claims, 4 Drawing Sheets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5400
4200
3000
1800
600
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG. 1

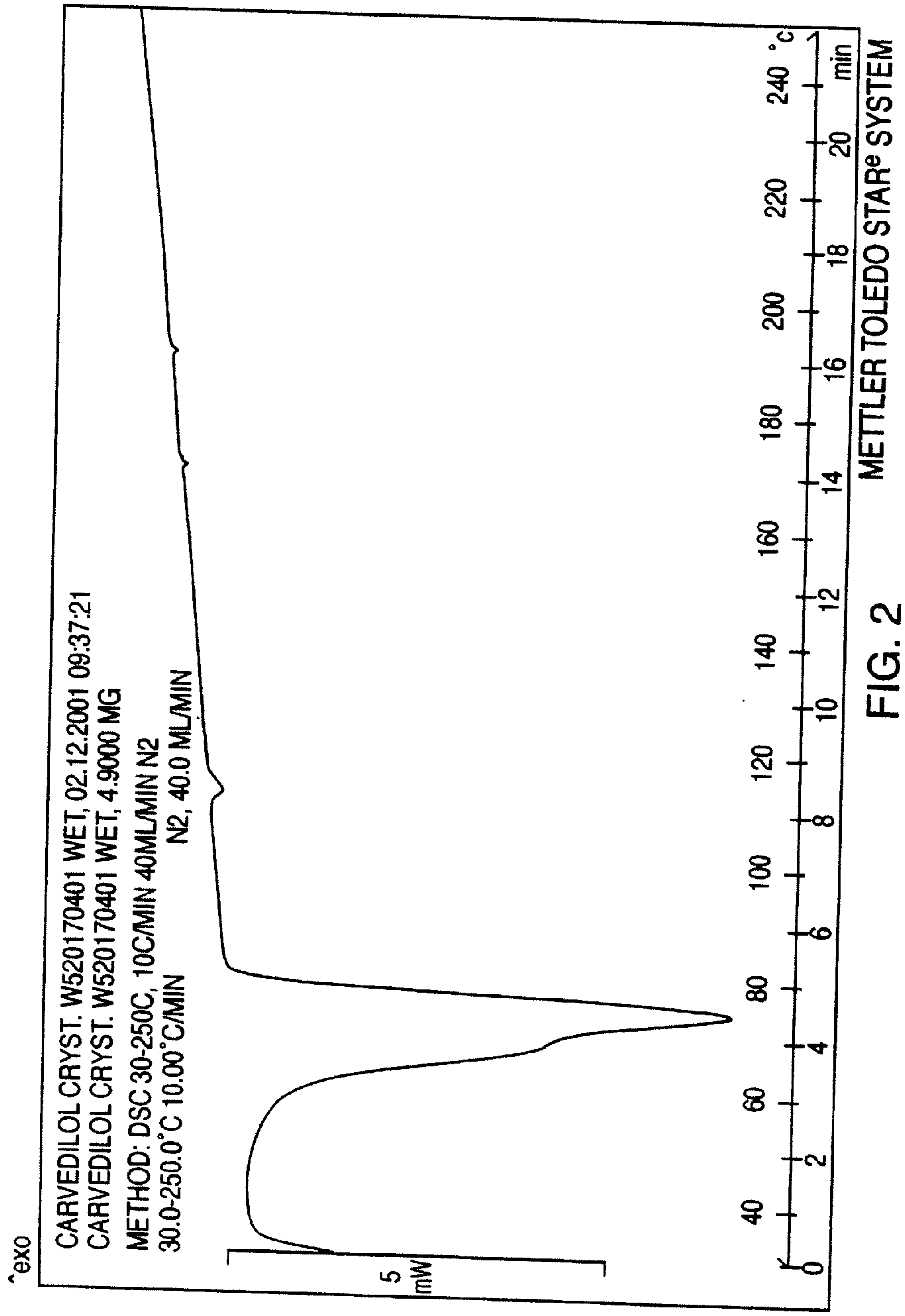
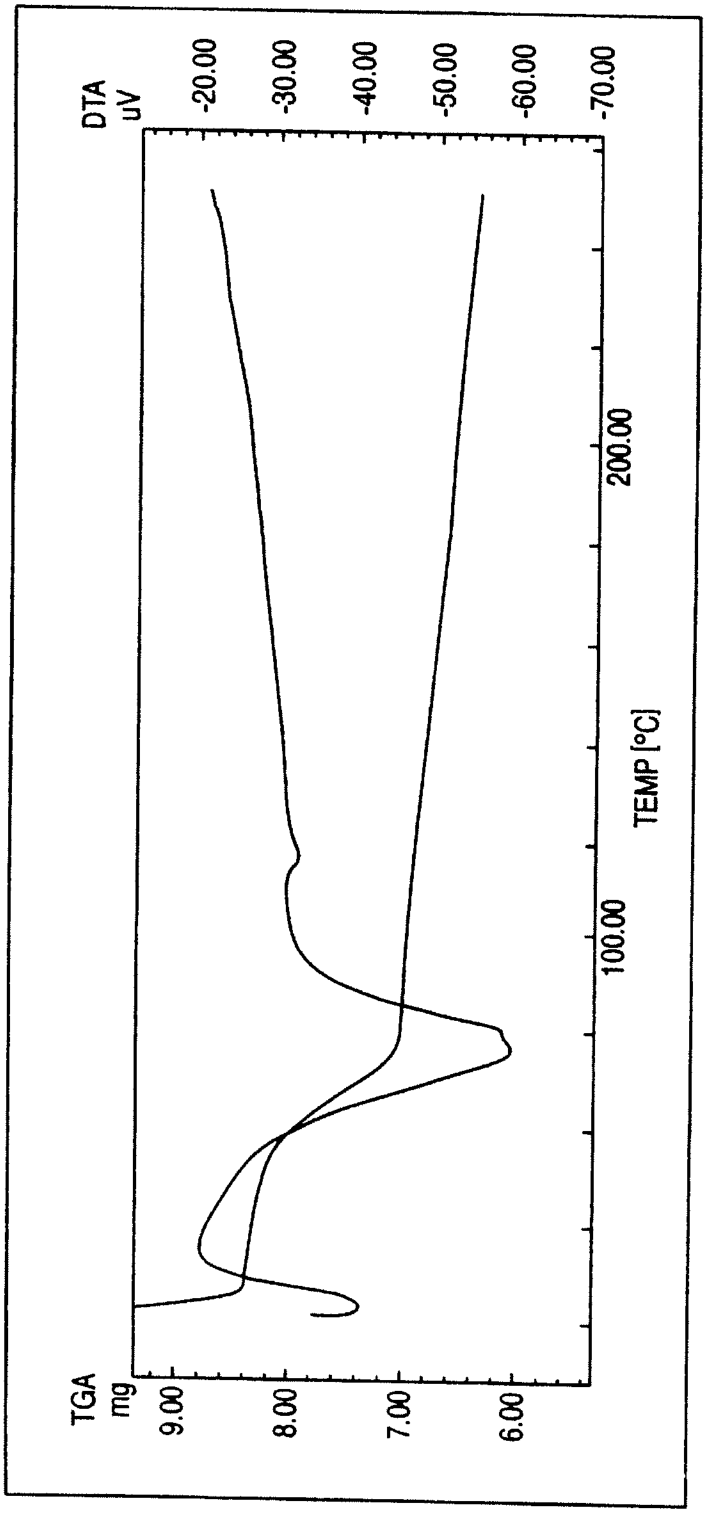

^exo
CARVEDILOL CRYST. W520170401 WET, 02.12.2001 09:37:21
CARVEDILOL CRYST. W520170401 WET, 4.9000 MG
METHOD: DSC 30-250C, 10C/MIN 40ML/MIN N2
30.0-250.0°C 10.00°C/MIN
N2, 40.0 ML/MIN
5 mW
40
60
80
100
120
140
160
180
200
220
240
°C
0
2
4
6
8
10
12
14
16
18
20
min
METTLER TOLEDO STARe SYSTEM

FIG. 2


DTA
uV
-20.00
-30.00
-40.00
-50.00
-60.00
-70.00
TGA
mg
9.00
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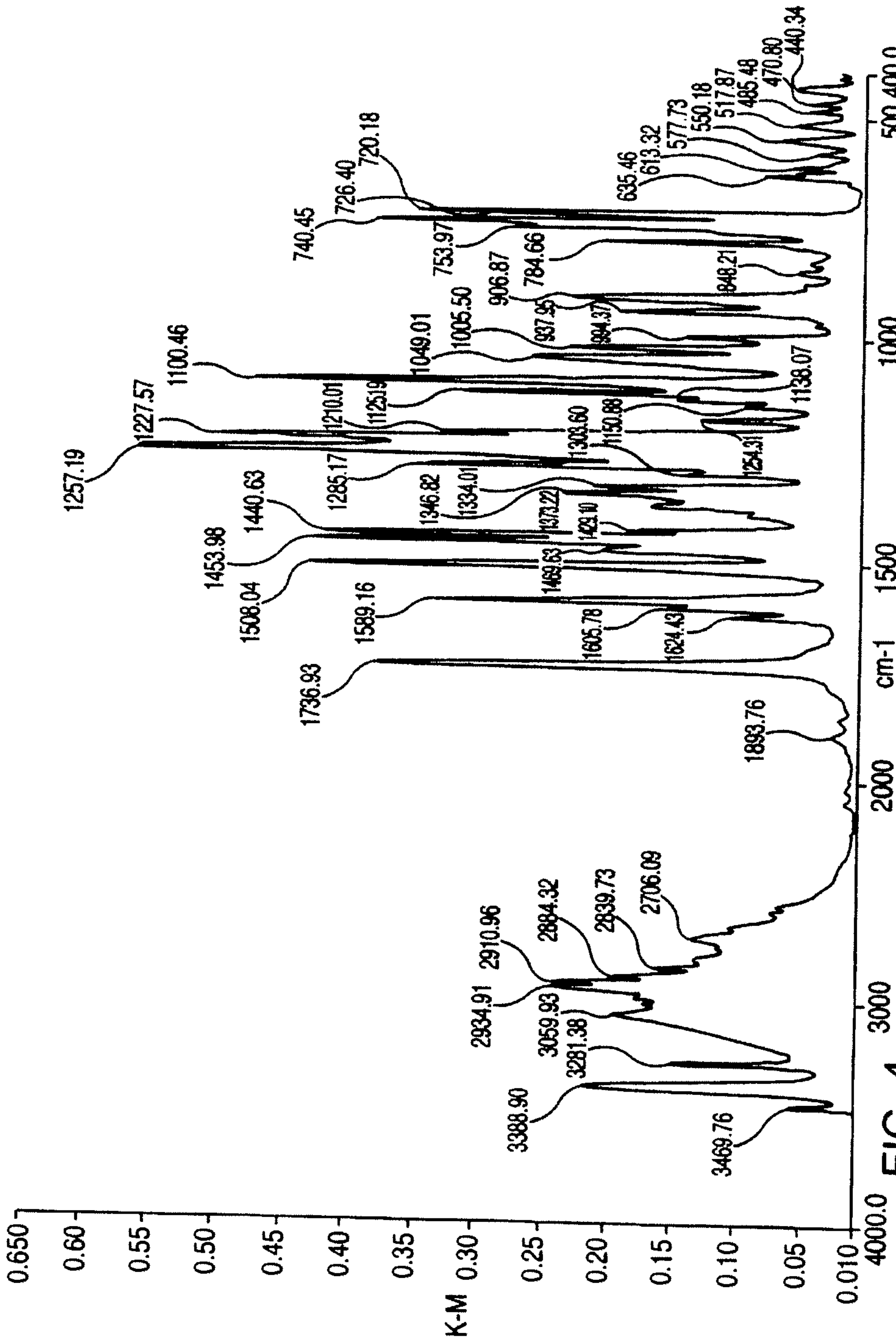
100.00
200.00
TEMP [°C]

FIG. 3



CARVEDILOL FORM VI

FIG. 4

CRYSTALLINE SOLIDS OF CARVEDILOL AND PROCESSES FOR THEIR PREPARATION

CROSS-REFERENCE TO RELATED APPLICATION

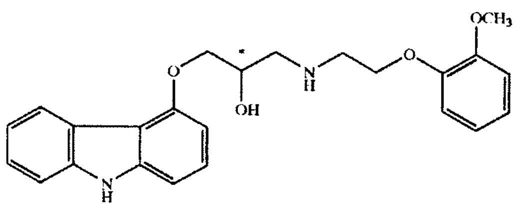
This application claims the benefit of U.S. provisional application Serial No. 60/349,310, filed Jan. 15, 2002, which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to a novel crystalline solid of carvedilol or a solvate thereof, to processes for its preparation, to compositions containing it and to its use in medicine. This invention further relates to a novel process for preparing crystalline carvedilol Form II.

BACKGROUND OF THE INVENTION

Carvedilol, (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy) ethyl]amino]-2-propanol, is a nonselective β-adrenergic blocker with α_1-blocking activity. Carvedilol is a racemic mixture having the following structural formula:



Carvedilol (I)

Carvedilol is the active ingredient of COREG®, which is indicated for the treatment of congestive heart failure and for the management of hypertension. Since carvedilol is a multiple-action drug, its beta-blocking activity affects the response to certain nerve impulses in parts of the body. As a result, beta-blockers decrease the heart's need for blood and oxygen by reducing its workload. Carvedilol is also known to be a vasodilator resulting primarily from alpha-adrenoceptor blockade. The multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug and for its effectiveness in managing congestive heart failure.

International application No. WO 99/05105 (the '105 application) discloses that carvedilol can be isolated in two polymorphic forms, depending on the method of preparation. The two polymorphic forms, designated Form I and Form II, are reported to be monotropic and are distinguishable by their infrared, Raman and powder X-ray diffraction (PXRD) spectra. No evidence is found in the literature about the existence of solvate forms of carvedilol.

In Example 1 of the '105 application, Form I was generated by dissolving crude carvedilol in methanol, heating the solution, cooling the solution, and stirring the solution for a time sufficient to produce Form I. Form II was generated by recrystallizing Form I in 2-propanol.

The present invention relates to the solid state physical properties of carvedilol. These properties can be influenced by controlling the conditions under which carvedilol is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. The polymorphic form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetric (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct spectroscopic properties that may be detectable by powder X-ray crystallography, solid state ^{13}C NMR spectrometry and infrared spectrometry.

The present invention also relates to solvates of carvedilol. When a substance crystallizes out of solution, it may trap molecules of solvent at regular intervals in the crystal lattice. Solvation also affects utilitarian physical properties of the solid state like flowability and dissolution rate.

One of the most important physical properties of a pharmaceutical compound, which can form polymorphs or solvates, is its solubility in aqueous solution, particularly the solubility in gastric juices of a patient. Other important properties relate to the ease of processing the form into pharmaceutical dosages, such as the tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet.

The discovery of new polymorphic forms and solvates of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. A new polymorphic form and solvate of carvedilol has been discovered.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a crystalline solid of carvedilol or a solvate thereof characterized by data selected from the group consisting of a PXRD pattern with peaks at about 6.5, 7.3, 16.0, and 30.5±0.2 degrees two-theta, a PXRD pattern with peaks at about 5.8, 10.7, 11.1, 11.5, 13.1, 13.7, 16.8, 17.7, 18.5, and 23.0±0.2 degrees two-theta, a DSC thermogram with endothermic peaks at about 74° C. and 112° C., and a FTIR spectrum with peaks

at about 613, 740, 994, 1125, 1228, 1257, 1441, 1508, 1737, 2840, 3281, 3389, and 3470 cm^{-1}. Said solid crystalline form denotes Form VI.

In another aspect, the present invention provides a process for preparing a crystalline solid of carvedilol or a solvate thereof having at least one characteristic of Form VI (such as the PXRD peaks and/or FTIR peaks, and/or DSC peaks disclosed herein). In accordance with the process, carvedilol is contacted with ethyl acetate to form a solution. The solution is cooled and optionally seeded with carvedilol Form II. The solution can be stirred under high velocity agitation to form a suspension, which then can be cooled under high velocity agitation.

In yet another aspect, the present invention provides a process for preparing a crystalline solid of carvedilol Form II, including the steps of heating crystalline carvedilol having at least one characteristic of Form VI until the crystalline carvedilol is dry, mixing carvedilol Form II with the dry crystalline carvedilol, and storing the mixture for a holding time sufficient to transform the dry crystalline carvedilol into Form II.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a PXRD pattern for carvedilol Form VI.

FIG. 2 is a FTIR spectrum for carvedilol Form VI.

FIG. 3 is a DSC thermogram for carvedilol Form VI.

FIG. 4 is a DTG thermogram for carvedilol Form VI.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention provides a novel crystalline solid of carvedilol or a solvate thereof, designated Form VI. Carvedilol solvate Form VI is characterized by a PXRD pattern (FIG. 1) with peaks at about 6.5, 7.3, 16.0, and 30.5±0.2 degrees two-theta. Further PXRD peaks were observed at about 5.8, 10.7, 11.1, 11.5, 13.1, 13.7, 16.8, 17.7, 18.5, and 23.0±0.2 degrees two-theta.

Carvedilol solvate Form VI produces a FTIR spectrum (FIG. 2) with characteristic absorption bands at about 613, 740, 994, 1125, 1228, 1257, 1441, 1508, 1737, 2840, 3281, 3389, and 3470 cm^{-1}. Further FTIR peaks were observed at about 720, 1100, 1286, 1454, 1589, 2911, and 2935 cm^{-1}.

Carvedilol solvate Form VI produces a DSC thermogram (FIG. 3) showing two endothermic peaks: the main endothermic peak was observed at about 74° C. and a minor endotherm (dH=0.7J/g) was observed at 112° C.

Carvedilol solvate Form VI produces a Differential Thermal Gravimetry (DTG) thermogram (FIG. 4) showing a weight loss step in the temperature range of 35–104° C. of about 13%. This value is equal to the expected value corresponding to two molecules of ethyl acetate per three molecules of carvedilol.

The water content of carvedilol solvate Form VI was tested by Karl-Fisher titration, which showed it to be free of water.

In another aspect, the present invention provides a novel process for preparing a crystalline solid of carvedilol or a solvate thereof, involving the steps of contacting carvedilol with ethyl acetate to form a solution, cooling the solution optionally under agitation. Preferably, the starting carvedilol is dry. The solution can optionally be seeded with carvedilol Form II. The solution can be stirred under high velocity agitation to form a suspension, which then can be cooled under high velocity agitation. The product obtained by this process has at least one characteristic of Form VI, and can be separated from the ethyl acetate by conventional means such as filtration. The product can also be dried.

Preferably, the mixture of ethyl acetate and dry carvedilol is heated to a temperature in the range of about 65° to about 80° C., most preferably in the range of about 70° to about 77° C. to form a solution. Thereafter, preferably, the temperature of the solution is reduced to between about 40° to about 55° C., most preferably between about 46° to about 50° C.

When the solution is seeded with carvedilol Form II, the seeded solution is stirred at a temperature in the range of about 46° C. to about 50° C. for a holding time sufficient to precipitate Form VI. A holding time of about 30 minutes under high velocity agitation (at least 260 rpm) is typically sufficient. Thereafter, the temperature of the suspension is preferably cooled to about 10° C. for a holding time, preferably about 3 hours under high velocity agitation. The cooled suspension should be stirred for about 30 minutes.

In another aspect, the present invention provides a process for preparing a crystalline solid of carvedilol Form II, including the steps of heating crystalline carvedilol having at least one characteristic of Form VI until the crystalline carvedilol is dry, mixing carvedilol Form II with the dry crystalline carvedilol, and storing the mixture for a holding time sufficient to transform the dry crystalline carvedilol into Form II.

Preferably, crystalline carvedilol having at least one characteristic of Form VI is heated to a temperate in the range of about 50° to about 60° C., and most preferably to about 55° C. The heating step can be preformed at atmospheric pressure or under reduced pressure. Preferably, the pressure is about 60 mm Hg, and more preferably about 30 mm Hg. Crystalline carvedilol having at least one characteristic of Form VI is typically dry after about 16 hours of heating.

Dry crystalline carvedilol having at least one characteristic of Form VI is mixed with carvedilol Form II and stored for a holding time sufficient to transform the dry crystalline carvedilol into Form II. A holding time of from about 1 week to about 2 weeks is typically sufficient. Carvedilol Form I can also be present.

Carvedilol Form VI can be milled into a powder and used in a pharmaceutical product or physically modified such as by granulation to produce larger granules of carvedilol Form VI. Carvedilol Form VI can also be used to prepare a liquid pharmaceutical product by dissolving or dispersing it in a liquid medium such as water, glycerin, vegetable oil and the like as discussed in greater detail below.

Carvedilol Form VI is useful for treating patients with congestive heart failure and hypertension and for producing a hypotensive effect in mammals, including human patients. Carvedilol Form VI can be formulated into a variety of compositions for administration to humans and mammals.

Pharmaceutical compositions of the present invention contain carvedilol Form VI, optionally in mixture with other crystalline forms and/or other active ingredients such as hydrochlorothiazide. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention can contain one or more excipients. Excipients are added to the composition for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition and can make a pharmaceutical dosage form containing the composition easier for the patient and caregiver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch,

calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form like a tablet can include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flow properties of non-compacted solid composition and improve the accuracy of dosing. Excipients that can function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product form the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, carvedilol Form VI and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that can be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention can also contain a viscosity-enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar can be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid can be added at levels safe for ingestion to improve storage stability.

A liquid composition according to the present invention can also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts to use can be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions.

Carvedilol Form VI can be administered for treatment of congestive heart failure and hypertension by any means that delivers the active ingredient(s) to the site of the body where beta-blocking activity exerts a therapeutic effect on the patient. For example, administration can be oral, buccal, parenteral (including subcutaneous, intramuscular, and intravenous) rectal, inhalant and ophthalmic. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. Carvedilol Form VI can be conveniently administered to a patient in oral unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts. Dosage forms include solid dosage forms like tablets, powders, capsules, sachets, troches and lozenges as well as liquid syrups, suspensions and elixirs.

The active ingredient(s) and excipients can be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filing can be prepared by wet granulation. In wet granulation some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump up into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate can then be tableted or other excipients can be added prior to tableting such as a glidant and or lubricant.

A tableting composition can be prepared conventionally by dry blending. For instance, the blended composition of

the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can be compressed subsequently into a tablet.

As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited to direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, only they are not subjected to a final tableting step.

Yet more particularly, a tablet can, for example, be formulated by blending and directly compressing the composition in a tablet machine.

A capsule can, for example, be prepared by filling half of a gelatin capsule with the above tablet composition and capping it with the other half of the gelatin capsule.

A simple parenteral solution for injection can, for example, be prepared by combining carvedilol Form VI, sterile propylene glycol, and sterile water and sealing the composition in a sterile vial under sterile conditions.

Capsules, tablets and lozenges and other unit dosage forms preferably contain a dosage level of about 1 mg to about 100 mg of carvedilol Form VI.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as limiting the scope or spirit of the invention.

EXAMPLES

General

The powder X-ray diffraction patterns were obtained by methods known in the art using a SCINTAG powder X-ray diffractometer model XTRA, variable goniometer, equipped with a solid-state detector. Copper radiation of λ=1.5418 Å was used. The scanning parameters included: measurement range: 2–40 degrees two-theta; continuous scan; rate: 3 degrees/minute.

The thermogravimetric curves were obtained by methods known in the art using a Mettler Toledo DSC821^e. The weight of the samples was about 3–5 mg. The temperature range was from about 30° C. to at least 250° C., at the rate of 10° C./minute.

The thermogravimetric curves were also obtained by methods known in the art using a Shimadzu DTG-50. The temperature range was from about 30° C. to at least 250° C., at the rate of 10° C./minute. Samples were purged with nitrogen gas at a flow rate of 20 ml/min.

The FTIR spectra were obtained by methods known in the art, such as diffuse reflectance, using a Perkin-Elmer, Spectrum One FTIR Spectrometer. The scanning parameters were as follows: range: 4000–400 cm^{-1}, 16 scans, resolution: 4.0 cm^{-1}.

Example 1

Carvedilol Form VI

Dry carvedilol (7 Kg) was added to ethyl acetate (70 L) and heated to about 70–77° C. under agitation. After complete dissolution, the solution was cooled to about 46–50° C. under agitation. The solution was then seeded with carvedilol Form II and stirred at a temperature of about 46–50° C. for about 30 minutes under high velocity agitation (at least 260 rpm). The resulting suspension was cooled to a temperature of about 10° C. over a period of 3 hours under high velocity agitation. The suspension was stirred for an addition 30 minutes and then filtered to obtain carvedilol Form VI.

Example 2

Carvedilol Form II

Three trays containing carvedilol Form VI (1 Kg per tray) were inserted into a vacuum oven, heated to about 55° C. under vacuum of 30 mm Hg and dried for about 16 hours. Immediately after drying, the polymorphic content of the dried sample was a mixture of Form VI and Form II. After storage at room temperature for about 4 weeks, a mixture of Form I, Form II and Form VI were found.

What is claimed is:

1. A process for preparing a crystalline solid of carvedilol Form II comprising the steps of:

heating crystalline carvedilol or a solvate thereof characterized by data selected from the group consisting of a PXRD pattern with peaks at about 6.5, 7.3, 16.0, and 30.5±0.2 degrees two-theta; a DSC thermogram with endothermic peaks at about 74° C. and 112° C.; and a FTIR spectrum with peaks at about 613, 740, 994, 1125, 1228, 1257, 1441, 1508, 1737, 2840, 3281, 3389, and 3470 cm^{-1} until the crystalline carvedilol is dry, mixing carvedilol Form II with the dry crystalline carvedilol, and storing the mixture for a holding time sufficient to transform the dry crystalline carvedilol into Form II.

2. The process of claim 1, wherein the crystalline carvedilol is heated to a temperature of from about 50° C. to about 60° C.

3. The process of claim 2 wherein the heating step is performed under reduced pressure.

4. The process of claim 3 wherein the pressure is at about 30 mm Hg.

* * * * *

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Exhibit D

US007056942B2

(12) **United States Patent**
Hildesheim et al.

(10) **Patent No.:** **US 7,056,942 B2**
(45) **Date of Patent:** **Jun. 6, 2006**

(54) **CARVEDILOL**

(75) Inventors: **Jean Hildesheim**, Mazkeret Batya (IL); **Sergey Finogueev**, Quiriat Arbaa (IL); **Judith Aronhime**, Rechovot (IL); **Ben-Zion Dolitzky**, Petach Tikva (IL); **Shoshana Ben-Valid**, Sderot (IL); **Ilan Kor**, Shoham (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 153 days.

(21) Appl. No.: **10/758,025**

(22) Filed: **Jan. 16, 2004**

(65) **Prior Publication Data**

US 2004/0152757 A1 Aug. 5, 2004

Related U.S. Application Data

(62) Division of application No. 09/894,798, filed on Jun. 28, 2001, now Pat. No. 6,699,997.

(60) Provisional application No. 60/214,356, filed on Jun. 28, 2000, and provisional application No. 60/246,358, filed on Nov. 7, 2000.

(51) **Int. Cl.**
C07D 209/82 (2006.01)
A61K 31/403 (2006.01)

(52) **U.S. Cl.** **514/411**; 548/444

(58) **Field of Classification Search** 548/440, 548/444; 514/411
See application file for complete search history.

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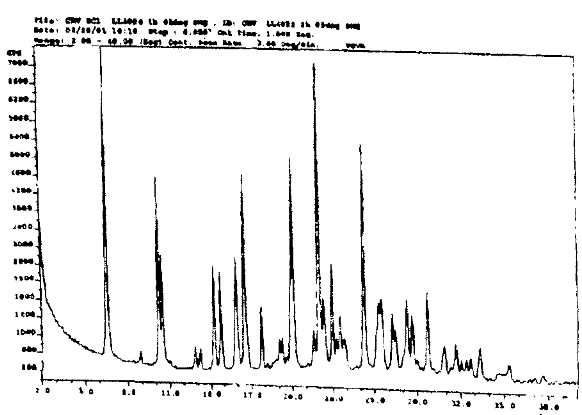
Primary Examiner—Kamal A. Saeed
Assistant Examiner—Janet L Coppins
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof.

5 Claims, 7 Drawing Sheets



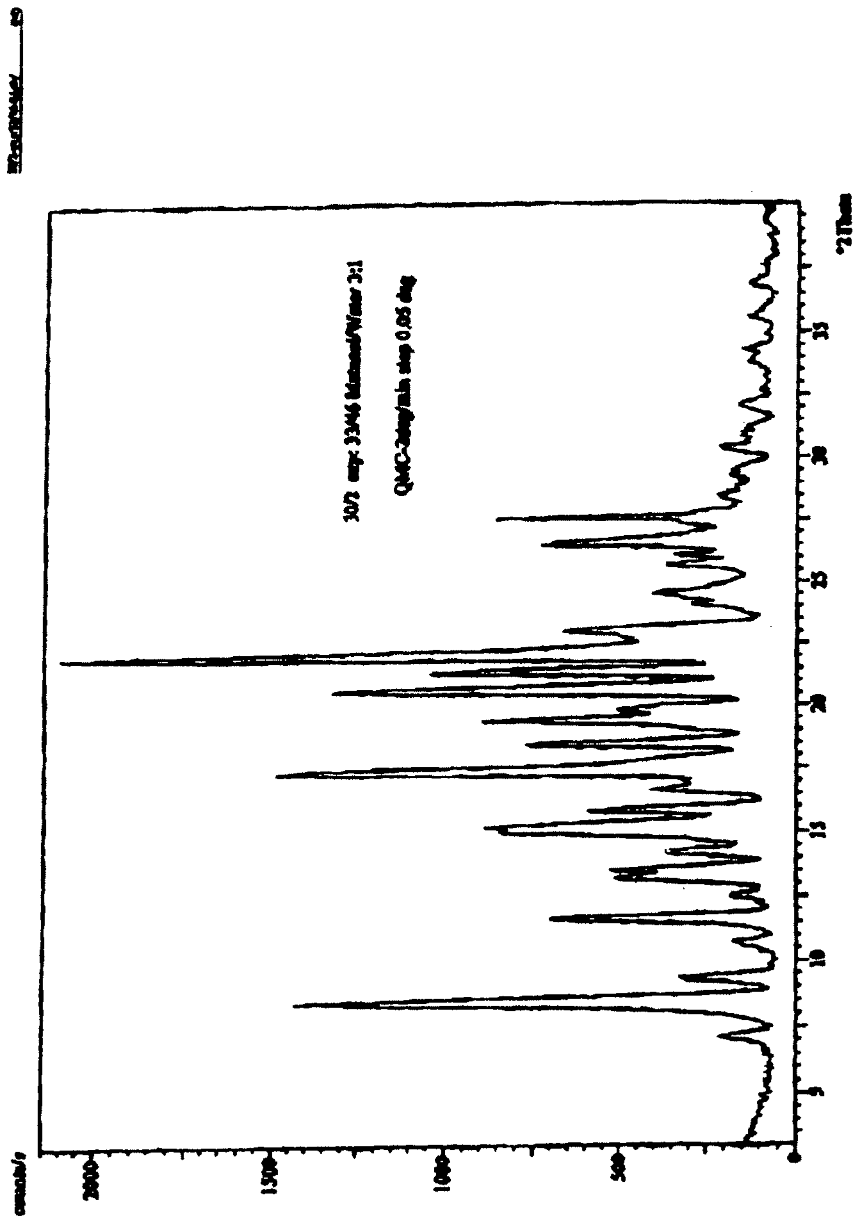
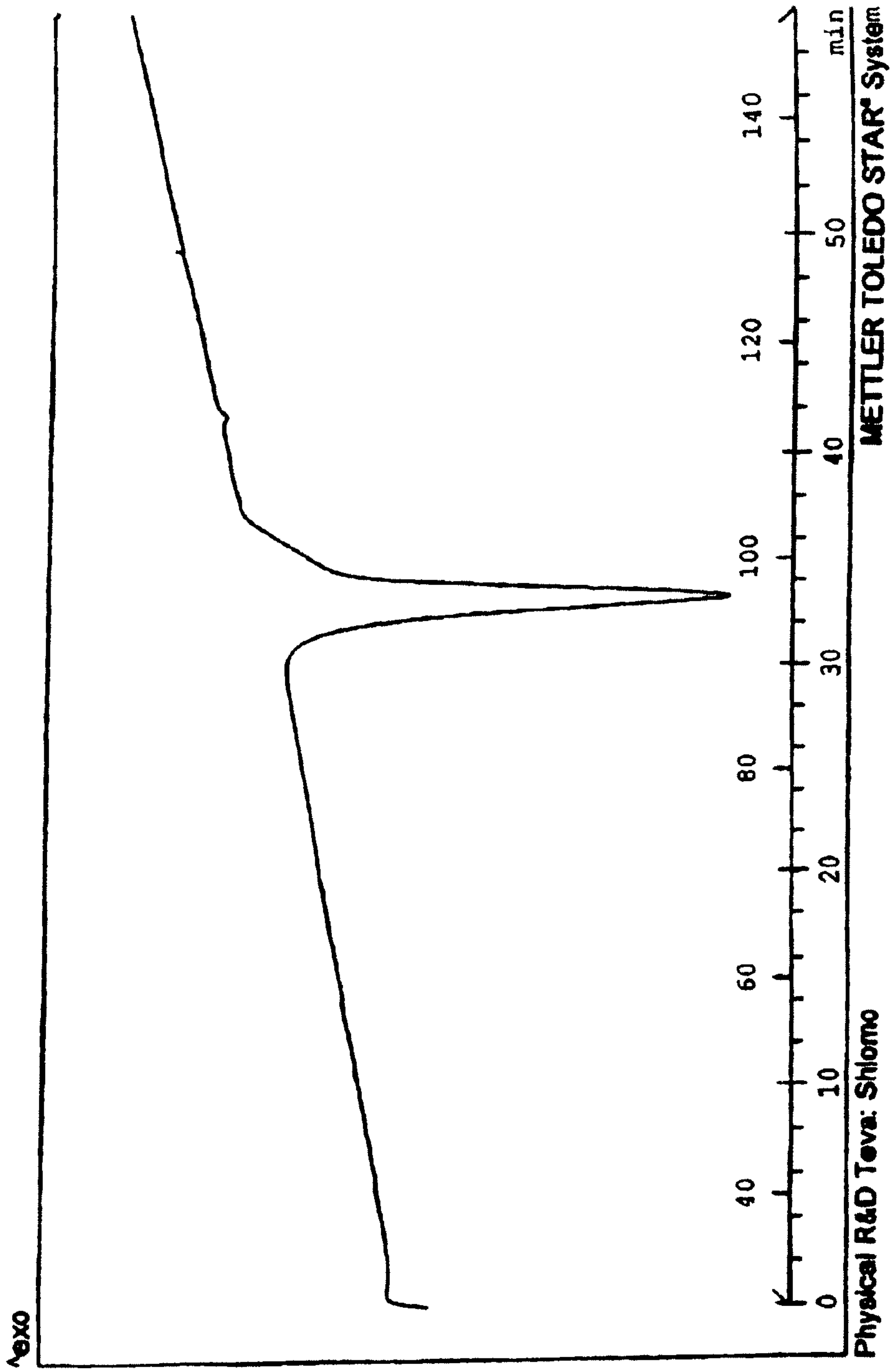


Figure 1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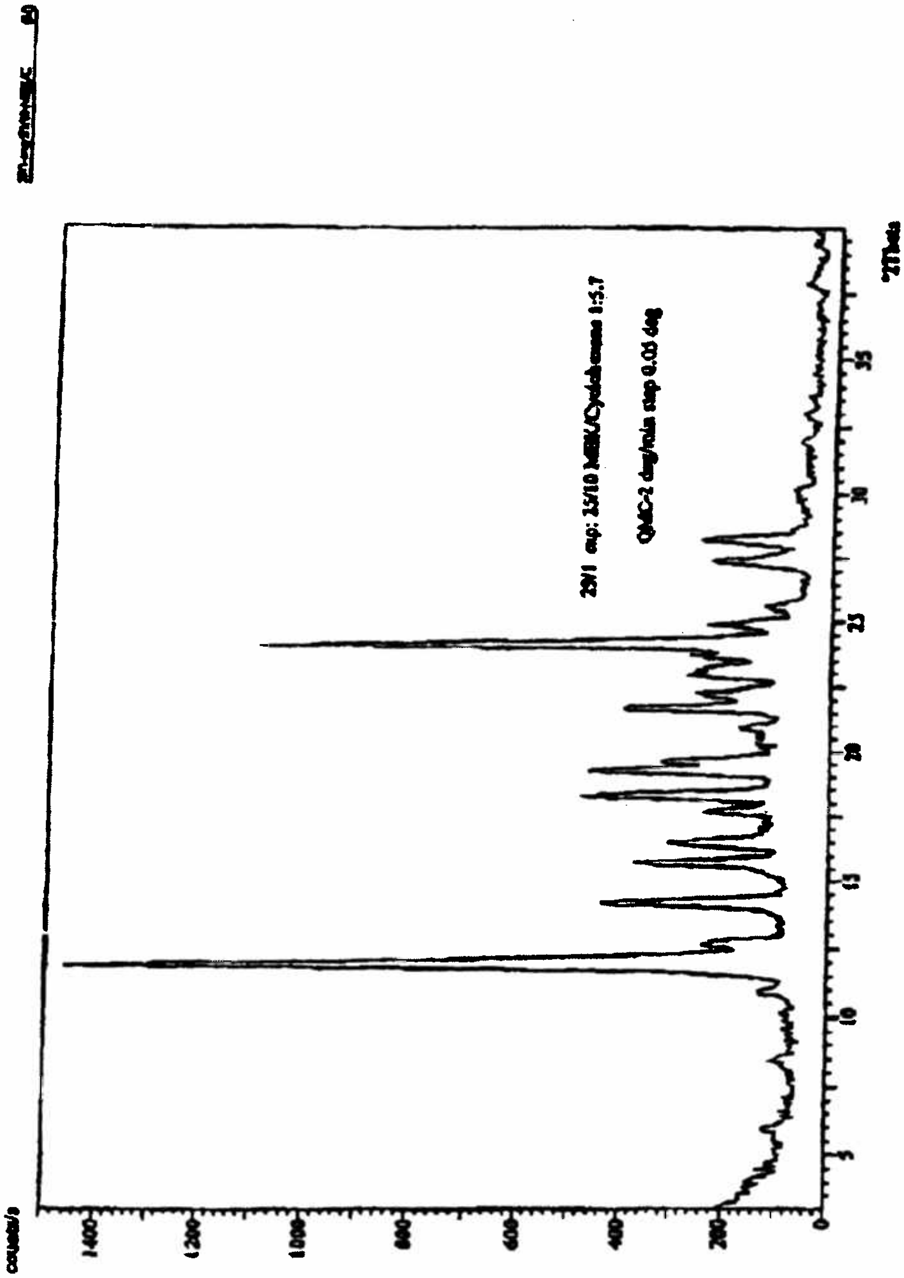
Physical R&D Teva: Shlomo
METTLER TOLEDO STAR® System

Figure 2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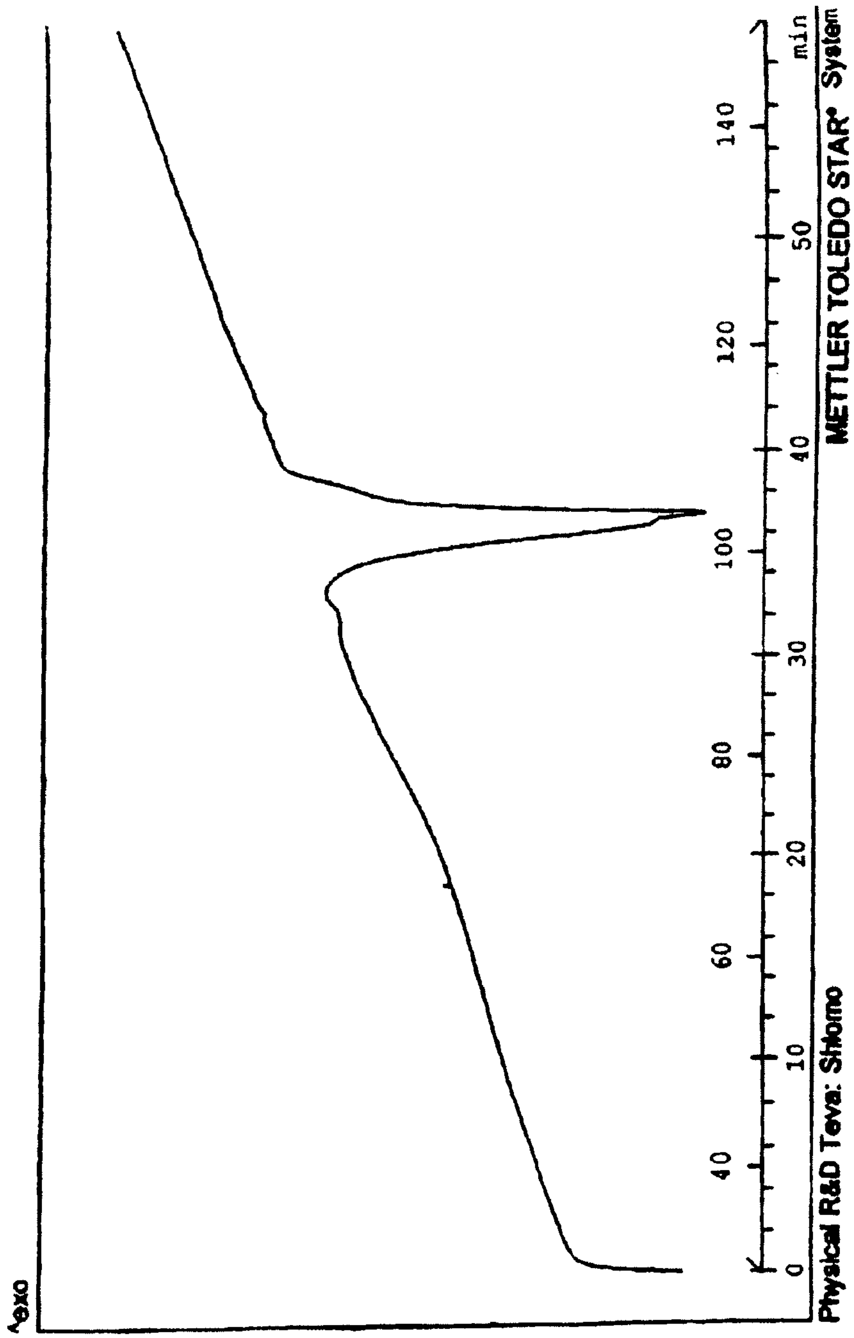
10
15
20
25
30
35
°2Theta
29/1 exp: 25/10 MIBK/Cyclohexane 1:5.7
QMC-2 deg/min step 0.05 deg

Figure 3



exo
0
40
10
60
20
80
30
100
40
120
50
140
min
Physical R&D Teva: Shlomo
METTLER TOLEDO STAR® System

Figure 4

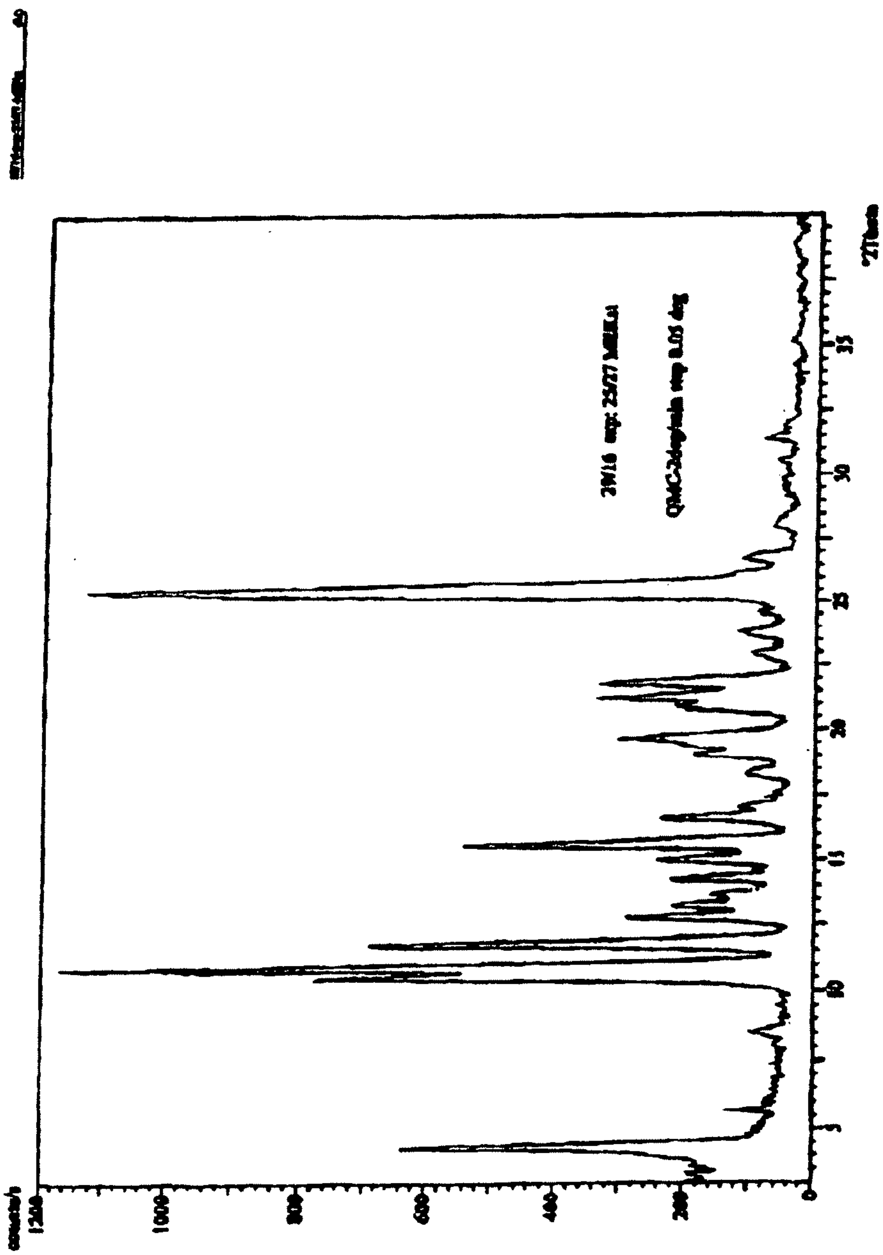


Figure 5

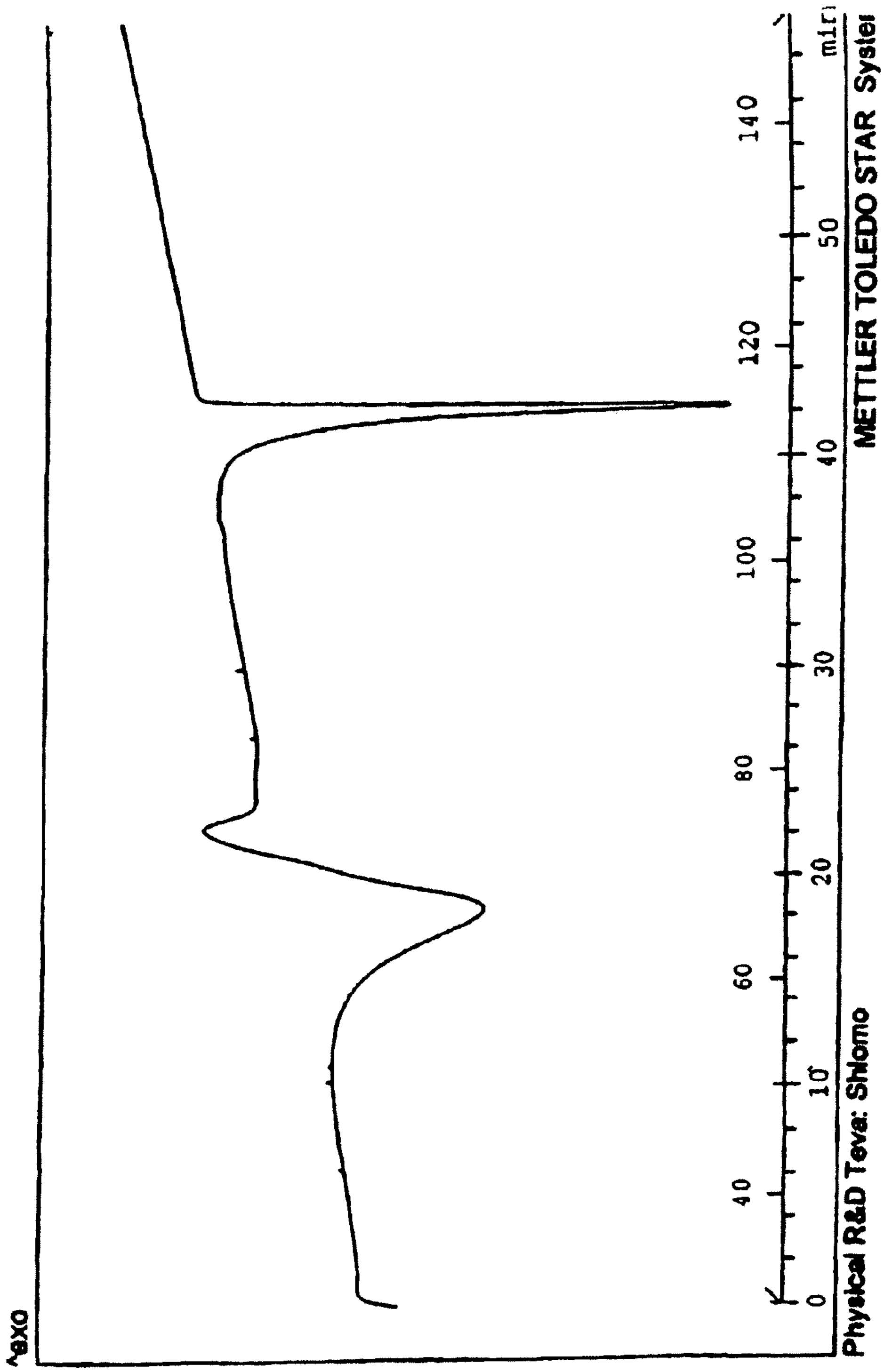

^exo
0
40
60
80
100
120
140
10
20
30
40
50
min
Physical R&D Teva: Shlomo
METTLER TOLEDO STAR System

Figure 6

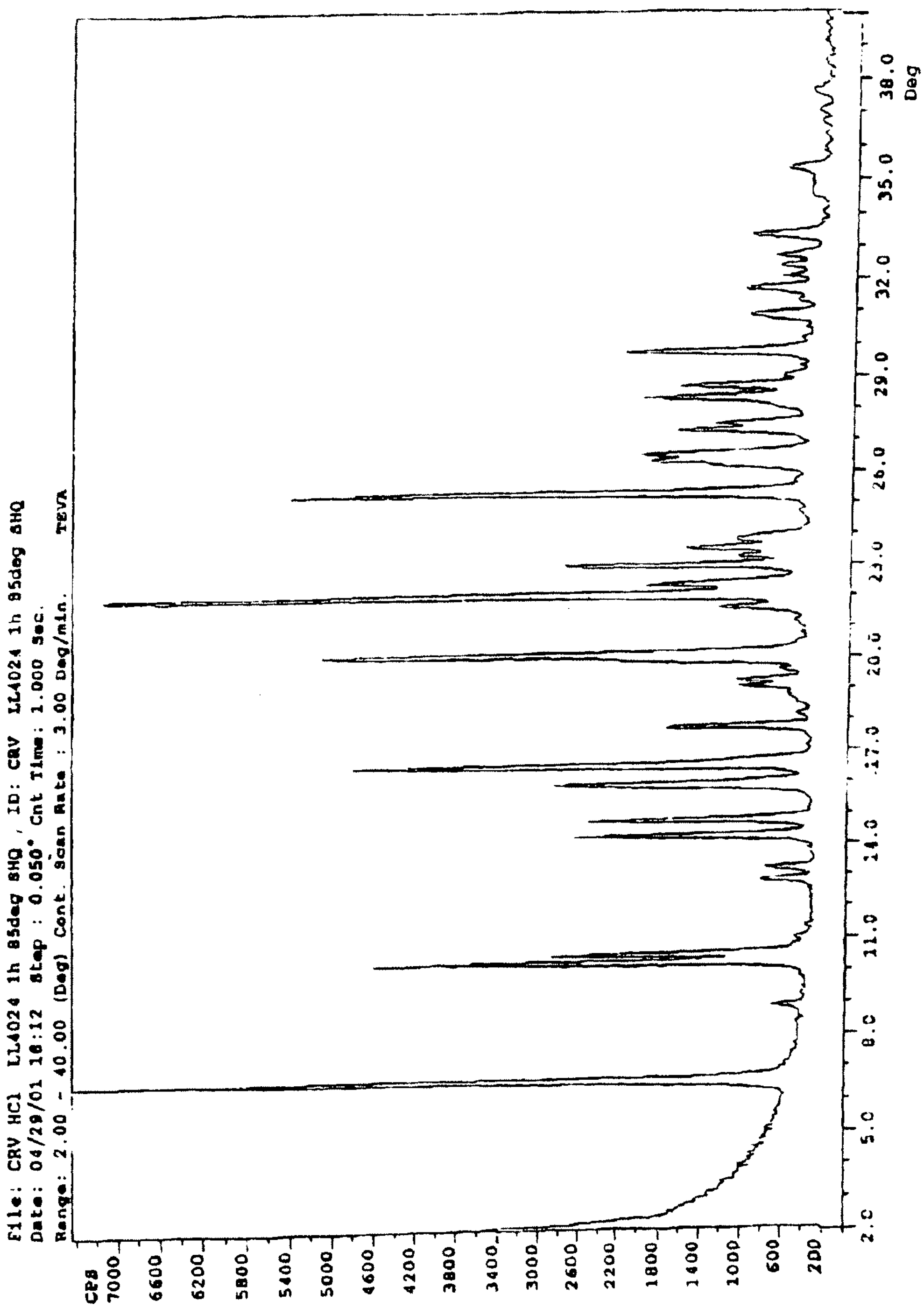

File: CRV HCl LL4024 1h 85deg 8HQ , ID: CRV LL4024 1h 85deg 8HQ
Date: 04/29/01 18:12 Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
7000
6600
6200
5800
5400
5000
4600
4200
3800
3400
3000
2600
2200
1800
1400
1000
600
200
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg

Figure 7

CARVEDILOL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of application Ser. No. 09/894,798 filed Jun. 28, 2001, now U.S. Pat. No. 6,699,997 and claims the benefit of U.S. provisional application Ser. No. 60/349,310, filed Jan. 15, 2002, which is incorporated herein by reference.

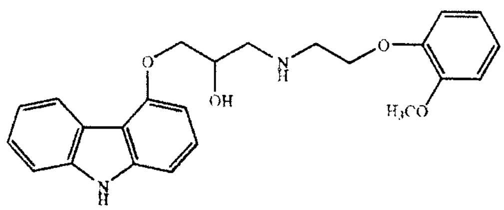
FIELD OF THE INVENTION

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

Carvedilol is a nonselective β-adrenergic blocking agent with α_1 blocking activity. Carvedilol, also known as (±) 1-(9H-carbazol-4-yloxy)-3-[[2(2-methoxyphenoxy)ethyl] amino]-2-propanol, (CAS Registry No. 72956-09-3) has the structure of formula I.

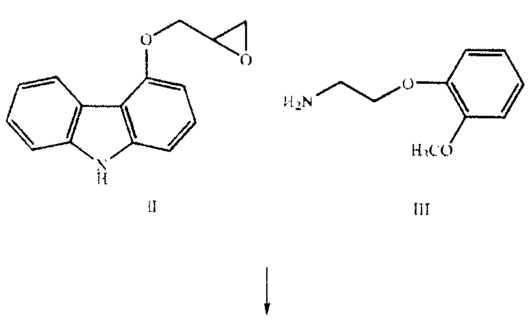
I



Carvedilol has a chiral center and can exist either as individual stereoisomers or in racemic form. Racemic carvedilol is the active ingredient of COREG®, which is indicated for the treatment of congestive heart failure and hypertension. The nonselective β-adrenergic activity of carvedilol is present in the S(−) enantiomer and the α_1 blocking activity is present in both the R(+) and S(−) enantiomers at equal potency. Both the racemate and stereoisomers may be obtained according to procedures well known in the art (EP B 0127 099).

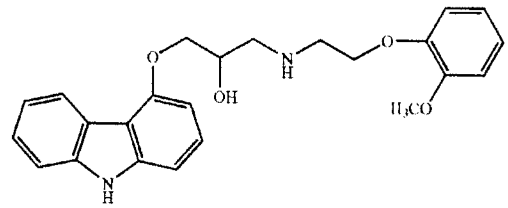
Synthesis of Carvedilol

U.S. Pat. No. 4,503,067, which is incorporated herein by reference, discloses a process of preparing carvedilol by the following reaction:



II III

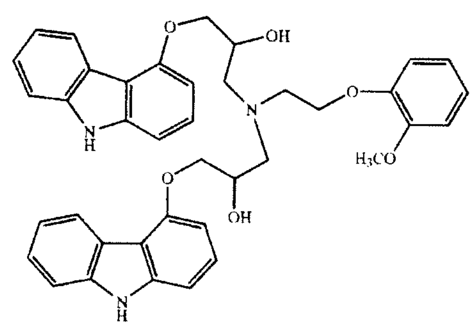
-continued



I

in which 4-(oxiran-2-ylmethoxy)-9H-carbazole (formula II) is reacted with (2-(2-methoxyphenoxy)ethylamine (formula III) to form carvedilol (I). The above process produces a low yield of carvedilol at least in part because in addition to carvedilol, the process leads to the production of a bis impurity of the following structure (formula IV):

IV



(See EP 918055.)

In order to reduce the formation of the formula IV and to increase the yield of carvedilol, EP 918055 discloses using a benzyl protected form of the 2-(2-methoxyphenoxy) ethylamine (III).

Carvedilol Polymorphs

International application No. WO 99/05105, incorporated herein by reference, discloses that carvedilol can be isolated as two polymorphic forms, depending on the method of preparation. The two polymorphic forms, designated Form I and Form II, are reported to be monotropic and are distinguishable by their infrared, Raman and X-ray powder diffraction spectra. No evidence is found in the literature about the existence of hydrated solvate states of carvedilol.

Polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline form in the solid state. A single molecule may give rise to a variety of crystal forms (also called "polymorphs," "hydrates," or "solvates") having distinct physical properties. For a general review of polymorphs and the pharmaceutical applications of polymorphs see *Pharm Manuf.*, 3, 33 (1986); J. K. Haleblian and W. McCrone, *J. Pharm. Sci.*, 58, 911 (1969); and J. K. Haleblian, *J. Pharm. Sci.*, 64, 1269 (1975), all of which are incorporated herein by reference.

The existence and physical properties of different crystal forms can be determined by a variety of techniques such as X-ray diffraction spectroscopy, differential scanning calorimetry and infrared spectroscopy. Differences in the physical properties of different crystal forms result from the orientation and intermolecular interactions of adjacent molecules (complexes) in the bulk solid. Accordingly, polymorphs, hydrates and solvates are distinct solids sharing

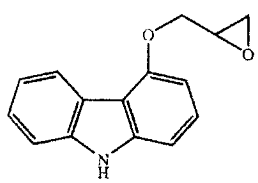
the same molecular formula yet having distinct advantageous and/or disadvantageous physical properties compared to other forms in the polymorph family. The existence and physical properties of polymorphs, hydrates and solvates is unpredictable.

One of the most important physical properties of a pharmaceutical compound which can form polymorphs, hydrates or solvates, is its solubility in aqueous solution, particularly the solubility in gastric juices of a patient. Other important properties relate to the ease of processing the form into pharmaceutical dosages, such as the tendency of a powdered or granulated form to flow and the surface properties that determine whether crystals of the form will adhere to each other when compacted into a tablet.

SUMMARY OF THE INVENTION

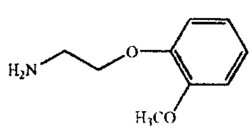
The present invention provides a process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,

II



with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine

III



wherein the compound of formula III is at a molar excess over the compound of formula II.

The present invention further provides crystalline carvedilol hydrate.

The present invention further provides crystalline carvedilol.

The present invention further provides crystalline carvedilol (methyl-ethyl-ketone) solvate.

The present invention further provides crystalline carvedilol Form III characterized by an X-ray powder diffraction pattern having peaks at about 8.4±0.2, 17.4±0.2, and 22.0±0.2 degrees two-theta.

The present invention further provides crystalline carvedilol Form IV characterized by an X-ray powder diffraction pattern having peaks at about 11.9±0.2, 14.2±0.2, 18.3±0.2, 19.2±0.2, 21.7±0.2, and 24.2±0.2 degrees two-theta.

The present invention further provides crystalline carvedilol (methyl-ethyl-ketone) solvate Form V characterized by an X-ray powder diffraction pattern having peaks at about 4.1±0.2, 10.3±0.2, and 10.7±0.2 degrees two-theta.

The present invention further provides carvedilol HCl Hydrate characterized by an X-ray powder diffraction pattern having peaks at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2, 16.4±0.2 and 22.2±0.2 degrees two-theta.

The present invention further provides a method for preparing crystalline carvedilol Form I, comprising the steps of dissolving carvedilol in a solution by heating; heating the solution until the crystalline carvedilol is completely dissolved; reducing the temperature of the solution; agitating the solution for a period of time; further reducing the temperature of the solution; further agitating the solution for a period of time; and collecting crystalline carvedilol Form I.

The present invention further provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent; precipitating carvedilol Form II by cooling the solution; and, isolating crystalline carvedilol Form II.

The present invention further provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent mixture; precipitating carvedilol Form II by cooling the solution to about −20° C.; and, isolating crystalline carvedilol Form II.

The present invention further provides a method for preparing crystalline carvedilol Form III, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating crystalline carvedilol Form III from the solvent solution using water as an anti-solvent.

The present invention further provides a method for preparing crystalline carvedilol Form III, comprising the steps of dissolving carvedilol in a solution by heating; cooling the solution mixture; and, collecting crystalline carvedilol Form III.

The present invention further provides a method for preparing crystalline carvedilol Form IV, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; adding an anti-solvent to the solvent solution; and, precipitating crystalline carvedilol Form IV from the solvent solution.

The present invention further provides a method for preparing crystalline carvedilol Form V, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating and isolating crystalline carvedilol Form V from the solvent solution.

The present invention further provides a method for preparing crystalline carvedilol Form V, comprising the steps of dissolving carvedilol in a solvent to form a solvent solution; and, precipitating and isolating crystalline carvedilol Form V from the solvent solution wherein the precipitation step is performed by adding an anti-solvent.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. shows the X-ray diffraction pattern of carvedilol Form III.

FIG. 2. shows the DTG thermal profile of carvedilol Form III.

FIG. 3. shows the X-ray diffraction pattern of carvedilol Form IV.

FIG. 4. shows the DTG thermal profile of carvedilol Form IV.

FIG. 5. shows the X-ray diffraction pattern of carvedilol Form V.

FIG. 6. shows the DTG thermal profile of carvedilol Form V.

FIG. 7. shows the X-ray diffraction pattern of carvedilol HCl.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "carvedilol" includes hydrates and solvates of carvedilol. The term "water content" refers

to the content of water, based upon the Loss on Drying method (the "LOD" method) as described in Pharmacopeia Forum, Vol. 24, No. 1, p. 5438 (January–February 1998), the Karl Fisher assay for determining water content or thermogravimetric analysis (TGA). The term "equivalents of water" means molar equivalents of water. All percentages herein are by weight unless otherwise indicated. Those skilled in the art will also understand that the term "anhydrous", when used in reference to carvedilol, describes carvedilol which is substantially free of water. One skilled in the art will appreciate that the term "hemihydrate", when used in reference to carvedilol, describes a crystalline material having a water content of about 2.2% w/w. One skilled in the art will appreciate that the term "hydrate" in reference to carvedilol hydrochloride a crystalline material having a water content of about or above 2% w/w. One skilled in the art will also appreciate that the term "solvate of methyl-ethyl-ketone" refers to carvedilol in which solvent is contained within the crystal lattice in quantities above 1%. One skilled in the art will also appreciate that the term "solvate of methyl-ethyl-ketone" which contains one mole of is characterized by a methyl-ethyl-ketone content of about 14% by weight.

Hydrate and solvate forms of carvedilol are novel and distinct from each other in terms of their characteristic powder X-ray diffraction patterns and their thermal profiles.

For the purposes of this specification, ambient temperature is from about 20° C. to about 25° C.

All powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer. Copper radiation of λ=1.5418 Å was used.

Measurement of thermal analysis are conducted for the purpose of evaluating the physical and chemical changes that may take place in a heated sample. Thermal reactions can be endothermic (e.g., melting, boiling, sublimation, vaporization, desolvation, solid-solid phase transitions, chemical degradation, etc.) or exothermic (e.g., crystallization, oxidative decomposition, etc.) in nature. Such methodology has gained widespread use in the pharmaceutical industry in characterization of polymorphism. Thermal measurements have proven to be useful in the characterization of polymorphic systems. The most commonly applied techniques are thermogravimetry (TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC).

The DTA and TGA curves presented herein were obtained by methods known in the art using a DTG Shimadzu model DTG-50 (combined TGA and DTA). The weight of the samples was about 9 to about 13 mg. The samples were scanned up to about 300° C. or above at a rate of 10° C./min. Samples were purged with nitrogen gas at a flow rate of 20 ml/min. Standard alumina crucibles covered lids with one hole.

Thermogravimetry analysis (TGA) is a measure of the thermally induced weight loss of a material as a function of the applied temperature. TGA is restricted to transitions that involve either a gain or a loss of mass, and it is most commonly used to study desolvation processes and compound decomposition.

Karl Fisher analysis, which is well known in the art, is also used to determine the quantity of water in a sample.

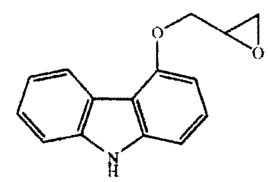
As used herein, a solvent is any liquid substance capable of dissolving carvedilol. As used herein, the term "anti-solvent" means a liquid in which a compound is poorly soluble. The addition of an anti-solvent to a solvent reduces the solubility of a compound. As used herein a mixture of solvents refers to a composition comprising more than one solvent.

As used herein, the term "neat" conditions refers to conditions of a reaction wherein the solvent of the reaction is one of the reactants.

Synthesis of Carvedilol

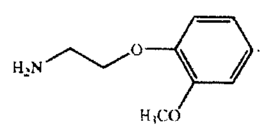
According to one embodiment, the present invention is a process for preparing carvedilol comprising a step of reacting a compound of formula II, 4-(oxiran-2-ylmethoxy)-9H-carbazole,

II



with a compound of formula III, 2-(2-methoxyphenoxy) ethylamine

III



The new procedure results in a higher yield of carvedilol than has been reported in the prior art. In addition, the product of the new procedure is nearly free of bis impurities and the reaction is more rapid.

Preferably, the compound of formula III is at a molar excess over the compound of formula II. The compound of formula III and the compound of formula II are preferably at a molar ratio from about 1.5:1 to about 100:1. More preferably, the compound of formula III and the compound of formula II are at a molar ration from about 2.8:1 to about 10:1. Most preferably, the compound of formula III and the compound of formula II are at a molar ratio from about 2.8:1 to about 6:1.

In one embodiment of the present invention, the reacting step is performed in a solvent. The solvent is preferably selected from the group consisting of toluene, xylene and heptane. In an alternative embodiment, the reacting step is performed in a solvent mixture wherein the solvent mixture comprises multiple solvents. Preferably, a solvent of the solvent mixture is selected from the group consisting of toluene, xylene and heptane.

The reacting step is preferably performed at a temperature from about 25° C. and about 150° C. Most preferably, the reacting step is performed at a temperature from about 60° C. and about 120° C.

In an alternative embodiment, the reacting step is performed under neat conditions. The neat conditions may obtained by melting a solid form of the compound of formula III to form a liquid and, dissolving the compound of formula II in the liquid to form a reaction mixture.

The reaction performed under neat conditions may further comprise a step of reducing the temperature of the reaction mixture after dissolving the compound of formula II. The temperature is preferably reduced to about 70° C.

The reaction performed under neat conditions may further comprise a step of adding an organic solvent: water mixture to the reaction mixture. The organic solvent is preferably selected from the group consisting of ethyl acetate, methyl isobutyl ketone, methyl ethyl ketone and butyl acetate.

The reaction performed under neat conditions may further comprise a step of adjusting the pH of the organic solvent: water mixture after it is added to the reaction mixture. The pH is preferably adjusted to less than about pH 5. More preferably, the pH is adjusted from about pH 3 to about pH 5.

Optionally, the process further comprises the steps of isolating carvedilol hydrochloride after adjusting the pH, and purifying carvedilol.

Carvedilol hydrochloride is optionally isolated as a hydrate. Carvedilol HCl isolated as a hydrate typically has an XRD peaks are found at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 14.2±0.2, 14.7±0.2, 16.4±0.2, 17.7±0.2, 20.0±0.2, 21.9±0.2, 25.2±0.2 degrees to 2-theta.

The reaction preformed under neat conditions may further comprise steps of, isolating carvedilol from the reaction mixture after adjusting the pH, and purifying carvedilol. Optionally, carvedilol may be purified by methods well known in the art. (See EP B 0127 099.)

Novel Methods for Preparing Crystalline Carvedilol Form I and Form II

One aspect of the present invention provides a method for preparing crystalline carvedilol Form I, by dissolving carvedilol in a solvent until the crystalline carvedilol is completely dissolved, reducing the temperature of the solution and agitating the solution for a period of time, further reducing the temperature of the solution and agitating the solution for a period of time and, collecting crystalline carvedilol Form I.

The dissolving step is optionally performed by heating the solvent.

The dissolving step is optionally performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

The dissolving step is optionally performed by suspending the crystalline carvedilol in ethyl acetate.

The dissolving step is optionally performed by heating the solution to about 77° C.

The step of reducing the temperature of the solution is optionally performed by cooling the solution to about 50° C. in a time period of 15 min.

The step of agitating solution is optionally performed at about 50° C. for about 48 hours.

The step of further reducing the temperature of the solution is optionally performed by cooling the solution to about 10° C. in about 0.75 hours with agitation.

The step of further agitating the solution is optionally performed by stirring the suspension for more than 5 hours. The step of further agitation may optionally be performed by stirring the suspension for about 24 hours.

The drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

The suspending step may be performed by suspending the crystalline carvedilol in ethyl acetate.

The heating step may be performed by heating the solution to about 77° C.

Another aspect of the present invention provides a method for preparing crystalline carvedilol Form II, comprising the steps of forming a solution of carvedilol by dissolving carvedilol in a solvent, precipitating carvedilol Form II by cooling the solution, and isolating crystalline carvedilol Form II.

Optionally, the step of dissolving carvedilol is performed at a temperature from about 40° C. to about the boiling temp of the solvent.

Optionally, the step of cooling the solution is performed by reducing the temperature from about −20° C. to about ambient temperature.

Optionally, the solvent is selected from the group consisting of methanol, absolute ethanol, 1-propanol, isopropanol, n-butanol, ethylene glycol, butyl acetate, isobutyl methyl ketone, dichloromethane, dichloroethane, acetonitrile, acetone, isoamylalcohol, xylene and toluene.

Optionally, the precipitated carvedilol Form II is isolated by filtration.

Another aspect of the present invention provides a method for preparing crystalline carvedilol Form II, comprising the steps of: forming a solution of carvedilol by dissolving carvedilol in a solvent mixture, precipitating carvedilol Form II by cooling the solution to about −20° C., and isolating crystalline carvedilol Form II.

Optionally, the carvedilol is dissolved in a solution at a temperature from about 40° C. to about the boiling temperature of the solvent.

Optionally, the carvedilol Form II is isolated by filtration.

Optionally, the step of cooling the reaction is performed by cooling the solution to a temperature from about −20° C. to ambient temperature.

Optionally, the solvent mixture is selected from the group consisting of acetone:cyclohexane, chloroform:cyclohexane, dichloroethane:cyclohexane, dichloromethane:cyclohexane, pyridine:cyclohexane, tetrahydrofuran:cyclohexane, dioxane:cyclohexane, acetone:hexane, chloroform:hexane, dichloroethane:hexane, dichloromethane:hexane, tetrahydrofuran:hexane and ethanol:hexane.

Novel Carvedilol Polymorphs

In another aspect the present invention provides new crystalline forms of carvedilol, designated Forms III, IV, V and processes for the manufacture thereof. Moreover, the present invention provides a new hydrate form of carvedilol, having water content of about 2% by weight and processes for their manufacture. In another embodiment, the present invention provides new solvate forms of carvedilol, having solvent content up to about 14% by weight, wherein the solvent is methyl ethyl ketone, and processes for their manufacture. These hydrate/solvate forms of carvedilol are useful as intermediates for the synthesis of carvedilol drug substances.

Procedures for Crystallizing Novel Forms of Carvedilol

The novel hydrates/solvates forms provided herein are optionally formed by precipitating carvedilol as a crystalline solid from a solvent or a solvent mixture. It will be understood by those of skill in the art, that other methods may also be used to form the hydrate/solvates form disclosed herein. Alternatively the polymorphs may be formed by routine modification of the procedures disclosed herein.

Formation of Crystalline Carvedilol Form III

One embodiment of the present invention provides a method for preparing crystalline carvedilol Form III, which comprises the steps of forming a solvent solution containing carvedilol; and, precipitating crystalline carvedilol Form III from the solvent solution using water as an anti-solvent. The invention provides for a dissolving step wherein water is present in the solvent solution during the dissolving step. The invention also provides for a precipitation step wherein water is added to the solution after carvedilol is fully dissolved in a solvent.

Optionally, to form the solvent solution containing carvedilol, carvedilol may be dissolved in a solvent at elevated temperature. The preferred elevated temperature is from about 40 to about 90° C. Most preferably the elevated temperature is about 55° C. Alternatively, carvedilol may be dissolved in a solvent at ambient temperature.

Another embodiment of the present invention provides, forming the solvent solution containing carvedilol, by dis-

solving carvedilol in a solvent and inducing precipitation of crystalline carvedilol Form III by the addition of an anti-solvent. Solvents are optionally selected from the group which includes pyridine, dioxane, isopropanol and chloroform. Anti-solvents are optionally selected from the group which includes water and hexane.

An alternative embodiment of the present invention provides, forming the solvent solution containing carvedilol by dissolving carvedilol in an organic solvent and water and precipitating crystalline carvedilol Form III. In this embodiment the organic solvent is optionally an alcohol. The alcohol is preferably selected from the group consisting of methanol and ethanol. Alternatively, the organic solvent may be selected from the group of solvents consisting of pyridine, dioxane, and ethyl acetate and tetrahydrofuran.

An alternative embodiment of the present invention provides, a method for preparing crystalline carvedilol Form III, comprising the steps of: drying crystalline carvedilol at elevated temperature, suspending crystalline carvedilol in a solution mixture, heating the solution mixture until the crystalline carvedilol is completely dissolved, cooling the solution mixture, and collecting crystalline carvedilol Form III.

Optionally, the drying step may be performed by heating crystalline carvedilol at a temperature from about 50° C. to about 60° C. for about 6 hours.

Optionally, the suspending step may be performed by suspending the crystalline carvedilol in a solution mixture of ethyl acetate: water (150:40).

Optionally, the heating step may be performed by heating the solution mixture from about 60 to about 70° C. with agitation until the crystalline carvedilol is completely dissolved.

Optionally, the cooling step may be performed by cooling the solution mixture to about to 10° C. for a period of about 3 hours with agitation.

Formation of Crystalline Carvedilol Form IV

The present invention also provides a method for preparing crystalline carvedilol Form IV by forming a solvent solution containing carvedilol and inducing precipitation of crystalline carvedilol Form IV by the addition of an "anti-solvent". In this embodiment, solvents are optionally selected from the group which includes methyl ethyl ketone, and methyl isobutyl ketone. Anti-solvents are optionally selected from the group which includes cylcohexane and heptane.

Optionally, to form crystalline carvedilol Form IV carvedilol may be dissolved in a solvent at from below ambient temperature to elevated temperatures. The preferred temperature is from about 10° to about 50° C. Most preferably the temperature is ambient temperature.

Formation of Crystalline Carvedilol Form V

The present invention also provides a method for preparing crystalline carvedilol Form V by forming a solvent solution containing carvedilol and inducing precipitation of crystalline carvedilol solvate Form V by cooling or by adding an anti-solvent. In this embodiment, the solvent is optionally selected from the group which includes methyl ethyl ketone. Anti-solvents are optionally selected from the group which includes cylcohexane and hexane.

Optionally, to form crystalline carvedilol Form V the carvedilol may be dissolved in a solvent solution at elevated temperature. The preferred elevated temperature is from about 10 to about 80° C. Most preferably the elevated temperature is about 55° C. Alternatively, carvedilol may be dissolved in a solvent solution at ambient temperature.

Novel Hydrate and Solvate Crystal Forms of Carvedilol

The present invention provides novel crystal forms of carvedilol which will be designated as Forms III, IV and V, as well as carvedilol HCl. These forms can be distinguished from the prior art forms of carvedilol and from each other by characteristic powder X-ray diffraction patterns and thermal profiles.

The different crystal forms may also be characterized by their respective solvation state. The most commonly encountered solvates among pharmaceuticals are those of 1:1 stoichiometry. Occasionally mixed solvate species are encountered. When water or solvent is incorporated into the crystal lattice of a compound in stoichiometric proportions, the molecular adduct or adducts formed are referred to as hydrates or solvates.

Crystalline Carvedilol Form III

Carvedilol Form III ("Form III") is characterized by an X-ray diffraction pattern with peaks at about 8.4±0.2, 9.3±0.2, 11.6±0.2, 13.2±0.2, 13.5±0.2, 14.2±0.2, 15.3±0.2, 15.8±0.2, 17.4±0.2, 18.4±0.2, 19.4±0.2, 20.6±0.2, 21.4±0.2, 22.0±0.2, 26.5±0.2 and 27.6±0.2 degrees two-theta. The most characteristic peaks of Form III are at about 8.4±0.2, 17.4±0.2, and 22.0±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 1.

The DTG thermal profile of Form IV is shown in FIG. 2. The differential scanning calorimetry (DSC) thermal profile of Form III shows one melting peak around 100° C. (96° C.–110° C.), depending on the samples and on the particle size. This melting peak is concomitant to a loss on drying of about 2% as measured by thermal gravimetric analysis (TGA). The amount of water in the sample as determined by Karl Fisher analysis is in good agreement with the value obtained from TGA, thus confirming that the loss on drying is due to the dehydration of water, and indicating that this material is a hemihydrate.

Crystalline Carvedilol Form IV

Carvedilol Form IV ("Form IV") is characterized by an X-ray diffraction pattern with peaks at about 11.9±0.2, 14.2±0.2, 15.7±0.2, 16.5±0.2, 17.7±0.2, 18.3±0.2, 19.2±0.2, 19.6±0.2, 21.7±0.2, 22.2±0.2, 23.9±0.2, 24.2±0.2, 24.9±0.2, 27.4±0.2 and 28.2±0.2 degrees two-theta. The most characteristic peaks of Form IV are at about 11.9±0.2, 14.2±0.2, 18.3±0.2, 19.2±0.2, 21.7±0.2, and 24.2±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 3.

The DTG thermal profile of Form IV is shown in FIG. 4. The DSC thermal profile of Form IV shows one melting peak at about 104° C.

Crystalline Carvedilol Form V

Carvedilol Form V ("Form V") is characterized by an X-ray diffraction pattern with peaks at about 4.1±0.2, 10.3±0.2, 10.7±0.2, 11.5±0.2, 12.6±0.2, 14.0±0.2, 14.8±0.2, 15.4±0.2, 16.4±0.2, 16.8±0.2, 18.8±0.2, 20.8±0.2, 21.1±0.2, 21.6±0.2, and 25.4±0.2, degrees two-theta. The most characteristic peaks of Form IV are at about 4.1±0.2, 10.3±0.2, 10.7±0.2 and 11.5±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 5.

The DTG thermal profile of Form V is shown in FIG. 6. The DSC thermal profile of Form V shows a solvent desorption endotherm at about 67° C., followed by a recrystallization event, and a melting peak at 115° C. The desorption endotherm is concomitant to a loss on drying of about 14% as determined by TGA. This behavior is consistent with the loss of a molecule of MEK per molecule of carvedilol (the calculated stoichiometric value of mono-MEK is 15%).

Carvedilol HCl Hydrate

Crystalline Carvedilol HCl is characterized by an X-ray diffraction pattern with peaks at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 14.2±0.2, 14.7±0.2, 15.8±0.2, 16.4±0.2, 17.7±0.2,

20.0±0.2, 21.5±0.2, 21.9±0.2, 22.2±0.2, 22.9±0.2, 25.2±0.2, 25.3±0.2, 27.2±0.2, 27.4±0.2, 28.2±0.2, 28.6±0.2, 29.6±0.2 degrees two theta. The most characteristic peaks of crystalline carvedilol HCl are at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2, 16.4±0.2 and 22.2±0.2 degrees two-theta. The diffraction pattern is reproduced in FIG. 7.

The DTG thermal profile of carvedilol HCl shows two endothermic peaks. A peak at 118° C. is a dehydration peak. A second peak endothermic peak at 135° C. is due to melting of the sample. LOD for this sample is 3.5%. The Water content of this sample as measured by Karl-Fisher analysis is 3.7%. Thus the Karl-Fisher analysis is in agreement with LOD value, and confirm the presence of hydrate in this sample. The expected value for carvedilol HCl monohydrate is 3.9%

A Pharmaceutical Composition Containing Carvedilol

According to another aspect, the present invention relates to a pharmaceutical composition comprising one or more of the novel crystal forms of carvedilol disclosed herein and at least one pharmaceutically acceptable excipient. Such pharmaceutical compositions may be administered to a mammalian patient in a dosage form.

The dosage forms may contain one or more of the novel forms of carvedilol or, alternatively, may contain one or more of the novel forms of carvedilol as part of a composition. Whether administered in pure form or in a composition, the carvedilol form(s) may be in the form of a powder, granules, aggregates or any other solid form. The compositions of the present invention include compositions for tableting. Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The novel forms of carvedilol disclosed herein also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The most preferred route of administration of the carvedilol forms of the present invention is oral.

Capsule dosages will contain the solid composition within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

The currently marketed form of carvedilol is available as a 3.125 mg, a 6.25 mg, a 12.5 mg, and a 25 mg tablet which includes the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

The function and advantage of these and other embodiments of the present invention will be more fully understood from the examples below. The following examples are intended to illustrate the benefits of the present invention, but do not exemplify the full scope of the invention.

EXAMPLES

Example 1

Preparation of Carvedilol in Neat Conditions

2-(2-Methoxyphenoxy)ethylamine (III) (4.89 g) was heated to about 100° C., after which 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (3.31 g) was added portionwise. After approximately 20 minutes, the reaction mixture was cooled to about 70° C., after which water (25 ml) and ethyl acetate (15 ml) were added. The pH of the two-phase mixture was then adjusted to 5 with 2 N hydrochloric acid. The solid that formed, Carvedilol hydrochloride hydrate, is filtered, washed with water (20 ml) followed with ethylacetate (15 ml).

The resulting material is reslurried in ethylacetate (50 mL) and water (20 mL) containing 5% sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4° C. Precipitated carvedilol was isolated by filtration and crystallized from isopropanol.

Example 2

Preparation of Carvedilol in Neat Conditions

2-(2-Methoxyphenoxy)ethylamine (III) (4.89 g) was heated to about 100° C., after which 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (3.31 g) was added portionwise. After approximately 20 minutes, the reaction mixture was cooled to about 70° C., after which water (25 ml) and ethyl acetate (15 ml) were added. The pH of the two-phase mixture was then adjusted to 5 with 2 N hydrochloric acid. The solid that formed, Carvedilol hydrochloride hydrate, is filtered, washed with water (20 ml) followed with ethylacetate (15 ml).

The resulting material is reslurried in ethyl acetate (50 mL) and water (20 mL) containing 5% sodium carbonate until the pH reached 7.5. The organic phase was separated and dried over sodium sulfate. The dried solution was concentrated to a turbid solution and cooled overnight to about 4° C. Precipitated carvedilol was isolated by filtration and crystallized from methanol.

Example 3

Process for Preparing Form I of Carvedilol

The dried crystalline carvedilol (220 g carvedilol) is dissolved in 2200 ml ethyl acetate. The ethyl acetate

solution is heated with agitation to 77° C. until the solid is completely dissolved. The ethyl acetate solution was then cooled with agitation to about 50° C. in a time period of 15 minutes. The cooled solution was stirred for 48 hours. The solution was then cooled to 10° C. in 0.75 hours with agitation. After stirring the suspension for additional 24 hours, the product was filtered. Pure Crystalline carvedilol Form I (170 g) was obtained.

Example 4

Preparation of Crystalline Carvedilol Form II

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table I. Carvedilol is crystallized by forming a solution of carvedilol heated to reach a clear solution, usually close to the solvent boiling temperature. The solution is then cooled to ambient temperature and the precipitate is filtered to yield carvedilol Form II.

TABLE I

Solvent	Ratio of Solvent (ml.):Carvedilol (g)
Methanol	11
Ethanol abs.	12
1-Propanol	14
Isopropanol	13
n-Butanol	11
Ethylene Glycol	13
Ethyl-Acetate	10
Butyl Acetate	12
Isobutyl Methyl Ketone	12
Dichloromethane	12
Dichloroethane	25
Acetonitrile	50
Acetone	25

Example 5

Preparation of Crystalline Carvedilol Form II by Filtration at −20° C.

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the solvents listed in Table II. Carvedilol is crystallized by forming a solution of carvedilol heated to about the solvent boiling temperature. The solution is then cooled to −20° C., the precipitate is filtered and dried to yield carvedilol Form II.

TABLE II

Solvent	Ratio of Solvent (ml): Carvedilol (g)
Isoamylalcohol	50
Toluene	53
Xylene	51

Example 6

Preparation of Crystalline Carvedilol Form II in Solvent Mixtures

Crystalline carvedilol Form II is formed by crystallizing carvedilol from the mixture of solvents listed in Table III. Carvedilol is crystallized by forming a solution of carvedilol heated to form a clear solution, usually close to the boiling temperature of the mixture of solvent. The solution is then cooled to ambient temperature and filtered. The crystals are collected by filtration and dried to yield carvedilol Form II.

TABLE III

Solvent	Solvents ratio	Ratio Solvent (ml): Carvedilol (g) [Please Confirm Units]
Acetone: Cyclohexane	1:4.8	230
Chloroform: Cyclohexane	1:3	130
Dichloroethane: cyclohexane	1:2.5	142
Dichloromethane: Cyclohexane	1:1.7	90
Pyridine: Cyclohexane	1:3.5	45
Tetrahydrofurane: Cyclohexane	1:2.5	53
Dioxane: Cyclohexane	1:2.3	70
Acetone:Hexane	1:2	235
Chloroform: hexane	1:1.5	87
Dichloroethane: Hexane	1:1.2	89
Dichloromethane: hexane	1:1.6	90
Tetrahydrofuran: Hexane	1:3	49
Ethanol:Hexane	1:3.8	145

Example 7

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 45 mL of a mixture of 96% Ethanol and 4% water by heating the mixture under stirring in a 55° C. water bath. The solution was cooled and left at room temperature without stirring for about 14 hours, the crystals were filtered through a buchner funnel, rinsed twice with about 10 ml cold (4° C.) 96% ethanol, and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 8

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 195 mL mixture of water/methanol (in a ratio 1:3 respectively) by heating the mixture under stirring in 55° C. water bath. The solution cooled to ambient temperature and left at ambient temperature without stirring for about 15 hours, the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected, to air pump) until constant weight to yield carvedilol Form III.

Example 9

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 39 ml. pyridine by stirring at room temperature. 70 mL of water was then added dropwise until crystallization began. The solution was left at room temperature without stirring for about 80 hours, then the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form III.

Example 10

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 76 mL dioxane at room temperature, and 110 mL of water were added in portions of about 10 mL to the stirred solution. The resulting solution was left at room temperature without stirring for about 15 h, then the crystalline precipitate which had formed was filtered through a buchner funnel and dried in desiccator at room temperature (connected to air pump) until constant weight to yield Carvedilol Form III in a mixture with Carvedilol Form II.

Example 11

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 267 mL dioxane/water in the ratio 1:1.4 respectively by heating the mixture under stirring at 55° C. water bath. The resulting solution was left at room temperature without stirring for about 15 h then the crystals were filtered through a buchner funnel and dried in a desiccator (connected to air pump) until constant weight to yield Carvedilol Form III in a mixture with Carvedilol Form II.

Example 12

Preparation of Crystalline Carvedilol Form III

Carvedilol (4 g) was dissolved in 180 ml, Hexane/IPA in a ratio 1:1 by heating the mixture under stirring at 55° C. water bath. The solution was allowed to sit at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator (connected to air pump) at room temperature until constant weight to yield Carvedilol Form III.

Example 13

Process for Preparing Form III of Carvedilol

Carvedilol (40 g) was dissolved in 150 ml of ethanol and 40 ml water. The solution was heated with agitation to 60 70° C. until the solid material was completely dissolved. The solution is then cooled with agitation to 10° C. over a period of 3 hours. After stirring the suspension for an additional 2.75 hours, the product is filtered. Pure Carvedilol Form III (35 g) was obtained.

Example 14

Preparation of Crystalline Carvedilol Form IV

Carvedilol (1 g) was dissolved in 35 mL methyl ethyl ketone by stirring at room temperature, and 202 mL cyclohexane was added dropwise. The solution was left at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form IV.

Example 15

Preparation of Crystalline Carvedilol Form V

Carvedilol (1 g) was dissolved in 70 mL methyl ethyl ketone by stirring at room temperature, and 138 mL hexane were added dropwise. The solution was left at room temperature without stirring for about 15 h, then the resulting crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form V.

Example 16

Preparation of Crystalline Carvedilol Form V

Carvedilol (2 g) was dissolved in 45 mL methyl ethyl ketone by heating the mixture under stirring at 55° C. water bath, then the solution was cooled and left at room temperature without stirring for about 14 hours, the crystals were filtered through a buchner funnel and dried in a desiccator at room temperature (connected to air pump) until constant weight to yield carvedilol Form V.

What is claimed is:

1. Carvedilol HCl Hydrate.

2. The carvedilol of claim 1 wherein the carvedilol HCl hydrate is crystalline.

3. The crystalline carvedilol of claim 2 characterized by an X-ray powder diffraction pattern having peaks at about 6.5±0.2, 10.2±0.2, 10.4±0.2, 15.8±0.2, 16.4±0.2 and 22.2±0.2 degrees two-theta.

4. The crystalline carvedilol of claim 3, further characterized by an X-ray powder diffraction pattern having peaks at about 14.2±0.2, 14.7±0.2, 16.4±0.2, 17.7±0.2, 20.0±0.2, 21.5±0.2, 21.9±0.2, 22.9±0.2, 25.2±0.2, 25.3±0.2, 27.2±0.2, 27.4±0.2, 28.2±0.2, 28.6±0.2, 29.6±0.2 degrees two theta.

5. The crystalline carvedilol of claim 2 characterized by a water content of about 3.5% by weight.

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